N/A

09/807345
PCT/DK 99/00562

REC'D 01 NOV 1999
WIPO PCT

Kongeriget Danmark

Patent application No.:	PA 1998 01320
Date of filing:	15 October 1998
Applicant:	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd

This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following document:

- The specification, claims, abstract, sequence listing, drawings and appendix I+II as filed with the application on the filing date indicated above.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patent- og Varemærkestyrelsen • Kongeriget Danmark

Patent- og Varemærkestyrelsen
Erhvervsministeriet

TAASTRUP 27 October 1999

Karin Schlichting
Head Clerk

AN IMPROVED METHOD for extracting quantitative information relating to an influence on a cellular response.

SUMMARY OF THE INVENTION

The present invention relates to an improved method and tools for extracting quantitative information relating to an influence on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, wherein the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to an improved method for extracting the quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. In particular, the present invention relates to an improved method for parallelisation of the testing procedure so that a large number of substances can be tested simultaneously using commercially available instrumentation. The invention also describes several ways of contacting the cells with a substance influencing a cellular response and modifications made to the actual cells before, during or after contacting the cells with these substances as to improve the applicability and use of the method for extracting quantitative information relating to influence on an intracellular pathway in a highly parallel fashion. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

Two appendices are included herein, and are considered part of the application. Appendix I, “METHOD AND APPARATUS FOR HIGH DENSITY FORMAT SCREENING FOR BIOACTIVE MOLECULES”, is a pending patent application. Appendix II, “CHANGES

IN INTRACELLULAR cAMP VISUALIZED USING A cAMP-DEPENDENT PROTEIN KINASE-GREEN FLUORESCENT PROTEIN HYBRID", is a manuscript intended for publication.

BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.* 1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for

protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi *et al.* 1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano *et al.* 1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. *et al.* 1995)] nucleus [(Khalil *et al.* 1992)], cytoskeleton [(Blobe *et al.* 1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil *et al.* 1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson *et al.* 1996)]; and c) chemical tagging of PKC β1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKC α([Schmidt *et al.* 1997]) and of PKC γ and PKC δ [(Sakai *et al.* 1996)]. The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit [(Adams *et al.* 1991)]. The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy

transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie *et al.* 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [(Carey, KL *et al.* 1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand

binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal. A similar genetic construct has been used to follow and quantify dexamethasone induced translocation of GR to the nucleus in HeLa cells [(Guiliano, K.A *et al.* 1997)] in a system called Array Scan™ (WO 97/45730) designed for automated drug screening. Recently, several other investigators have demonstrated that tagging a specific protein (or part of a protein) involved in an intracellular signalling pathway with GFP provides a new means to measure and quantify the influence of substances on this pathway. The concept has been shown to work both for cytoplasmic to nuclear translocation of the androgen receptor [(Georget V *et al.* 1997)] and transcription factors such as NF-ATc [(Beals CR *et al. 1997*)] in analogy with what has already been described for GR above. Another relevant example is a β-arrestin – GFP construct that was shown to report on activation of G-protein coupled receptors by translocating from the cytosol to the plasma membrane [(Barak LS *et al.* 1997)]. Finally, it has also been demonstrated that attaching GFP to a smaller part of a protein like the pleckstrin homology domain of phospholipase C δ 1 [(Stauffer TP *et al.* 1998)] and a cysteine-rich domain of PKC γ [(Oancea E *et al.* 1998)] can be used to report on an influence from a substance by quantifying their redistribution within the cells during activation of the specific signalling pathway to which they belong.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression. The interest in fluorescence measurements as the basis for future high-throughput drug screening has however increased dramatically over the last few years [(Silverman L *et al.* 1998)]. Of particular interest to the present invention is a scanning laser imager for rapid screening of fluorescence changes in living cells [(Schroeder K & Neagle B 1996)] currently offered commercially by Molecular Devices, Inc. as the FLIPR™.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the

redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilising the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to an improved method, with higher throughput compared to previous methods, for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In one aspect of the present invention the mechanically intact living cell is permeabilised at some

time after the influence has begun but during or before the actual experimental recording. In another aspect, the present invention relates to an improved method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on permeabilised living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cells are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time. In another embodiment the cell and/or cells are mechanically intact and alive throughout the experiment but are mechanically or chemically disrupted or permeabilised as the initial step of experimental analysis. In another aspect of the invention the cells have their plasma membrane permanently and stably permeabilised before the initiation of the experiment in such a way that the plasma membrane stays permeable during the experiment. This allows the components of intracellular pathways to be contacted by substances that are not normally permeating the cell plasma membrane such as peptides, proteins and hydrophilic organic compounds.

The mechanically intact or permeabilised living cells could be selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; and

vertebrate cells, such as mammalian cells. These cells are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact or permeabilised living cell is part of a matrix of identical or non-identical cells. In one embodiment of the invention the cells comprise a group or groups of cells contained within a spatial limitation or spatial limitations. In one embodiment, the cells comprise multiple groups of cells that are qualitatively the same but subjected to different influences. In another embodiment, the cells comprise multiple groups of cells that are qualitatively different but subjected to the same influence.

In one embodiment of the invention the spatial limitations are domains defined on a substrate on which the cells are present. The spatial limitations may be arranged in one or more arrays on a common carrier. The spatial limitations may be wells in a plate of microtiter type, such that 96, 384, 864 and 1536 wells are situated on the common carrier. In another embodiment the spatial limitations are wells in a plate of a format different from the microtiter type. In one embodiment of the invention the domains are established by the presence of the cells on the substrate in a pattern that defines the domains. In another aspect of the invention, the domains are instead established by the spatial pattern or array of the influence or influences as it/they are applied to or contacted by the cells. This aspect is thoroughly described in Appendix I. Briefly, in this aspect of the invention the mechanically intact or permeabilised living cells are part of a continuous or discontinuous sheet of cells cultured on an optically clear flat surface optimised or not for cell culture. The optically clear and flat surface may be a porous membrane that may allow cellular processes to grow through the membrane pores and may allow directed capillary flow of fluid through the pores.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

The luminophore is the component that allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. The term redistribution is intended to cover all aspects of a change in spatial location, such as a translocation of the luminophore or other components. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner that is physiologically relevant to the degree of the influence. It should be understood that redistribution. In another embodiment, the luminophore is capable of associating with a component that is capable of being redistributed in a manner that is physiologically relevant to the degree of the influence. In another embodiment, a correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component that is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence. In another embodiment of the invention, the luminophore is stationary but may have a certain spatial distribution, and interacts with at least one component that is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence, in such a way that one or more luminescence characteristics of the luminophore is/are modulated as the component moves closer to, or farther from, the luminophore.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as

defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of an intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

In a preferred embodiment of the invention, the influence could be contact between the group or groups of mechanically intact or permeabilised living cells and a chemical substance, and/or incubation of the group or groups of mechanically intact or permeabilised living cells with a chemical substance in solution. In one aspect of the invention that is thoroughly described in Appendix I, the chemical substances are attached to an underlying matrix. In this aspect, the chemical substances may also be produced and secreted from, or attached to the plasma membrane surfaces of, a sheet of genetically engineered cells. In this aspect of the invention the chemical substances may also have been separated two-dimensionally in a non-denaturing gel using electrophoresis and the gel is directly put in close proximity or direct contact with the mechanically intact or permeabilised living cells so that the chemical substances can contact the cells through diffusion or convection.

The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be a deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used to establish a dose-response relationship for one or many chemical substances. In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library,

can be compared to influence of known reference compounds under standardised conditions.

In addition to the intensity, there are several parameters of fluorescence or luminescence that can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, and wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon. In addition, the translational mobility, or freedom of movement, of the luminophore attached to the protein of interest can be an important property affected by the influence on the underlying cellular phenomena, and can therefore be used in he invention.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector that responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore includes the case of uniform spatial distribution of the light.

In one aspect of the invention, the luminophore is a fluorophore which redistributes through a non-homogenous excitation light field, resulting in a change in the intensity of the light emitted from the luminophore as a result of the change in the amount of excitation light intensity at different points in the field.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

In one embodiment the recording comprises a time series of total luminescence of the cells of one or several of the spatial limitations. In one embodiment the signal from all of the spatial limitations, one at a time, is measured by a recording being made in the individual spatial limitations by means of an apparatus to sequentially position each one of the limitations in the field of view of the detector and repeating the positioning and measurement process until all of the spatial limitations have been measured. The detector may be a photomultiplier tube. In a preferred embodiment of the present invention more than one spatial limitation is measured simultaneously. This may be done by means of a one- or two-dimensional array detector, whereby the multiple spatial limitations are imaged onto the array detector such that discrete subsets of the detecting units (pixels) in the array detector measure the signal from one and only one of the multiple spatial limitations, the signal from any one spatial limitation being the combined signal from those pixels that receive the image from one of the spatial limitations. This array detector may be a linear diode array, a video camera (according to any present or future standards and definitions of image acquisition and transmission) or a charge transfer device such as a charge-coupled device (CCD). In one embodiment the recording of signal requires

illumination of the multiple spatial limitations to excite the luminophores so that they emit light. In one embodiment all of the spatial limitations are simultaneously illuminated during the measurement. In another embodiment the spatial limitations are singly illuminated only during the time in which they are being measured. In a preferred embodiment the illumination is provided by a laser that is scanned in a raster fashion over some or all of the spatial limitations being measured. The scanning may take place at a rate that is substantially faster than the measurement process such that the illumination appears to the measurement process to be continuous in time and spatially uniform over the region being measured.

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cells, and thereby any change in the distribution of fluorescence in the cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the luminescence of the luminophore, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission (or another type of intensity map relevant to the method of detection and measurement), (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera. In one embodiment the component in f mentioned above is an array of photomultiplier tubes/devices.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment the optical scanning system is used to illuminate the bottom of a plate

of microtiter type so that a time-resolved recording of changes in luminescence or fluorescence can be made from all spatial limitations simultaneously.

In a preferred embodiment the actual luminescence or fluorescence measurements are made in a FLIPR™ instrument, commercially available from Molecular Devices, Inc.

In one embodiment of the invention the actual fluorescence measurements are made in a standard type of fluorometer for plates of microtiter type (fluorescence plate reader).

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

The methods whereby the detector layer of cells are physically contacted by the compounds can also be of another conceptual type where the compounds are delivered to the cells through a porous membrane by convection/diffusion or by directly contacting compounds attached to an inorganic or organic support (such as glass, plastic or the plasma membrane of intact living cells) with the cells. These methods are thoroughly described in Appendix I, but are also outlined in the following paragraphs.

In one aspect of the present invention where the detector layer of cells is a continuous or discontinuous sheet of cells without any separation into test units or wells. The compounds are printed onto a nonabsorbent sheet of porous material as a solution in solvent and allowed to dry. This printed sheet of compounds then defines the test pattern for the experiment as it is brought down in close proximity to or in direct contact with the underlying detector layer of cells. The compounds, now dissolved by the fluid layer on the cells, is brought in contact with the cells through the pores of the membrane by convection. The porous membrane onto which the compounds are printed is optically clear and preferably composed as stated in Appendix I. In another embodiment of this aspect of the present invention the detector layer of cells is a continuous or discontinuous sheet of cells, without any separation into test units or wells, growing on a porous and optically clear

membrane preferably of the types mentioned above. The porous membrane may allow the cells to send cellular processes through the pores of the membrane. The compounds are printed onto an optically clear substratum such as glass, plastic or quartz as solutions in solvent and allowed to dry. At the time of the experiment the cell sheet on the membrane, surrounded by a thin film of fluid, is layered ontop of the printed compound pattern. The compounds then dissolve and contact the cells via diffusion and convection. The compounds may be made using combinatorial chemistry techniques, and may be peptides. The compounds may be covalently attached to the optically clear substratum or porous membrane. The compounds may also be proteins, polypeptides or peptides secreted by or attached to the plasma membrane of genetically modified cells growing as a continuous or discontinuous sheet on a flat optically clear surface or an optically clear porous membrane.

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the response caused by the influence is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis), and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic

methods such as neural networks may also be used. In a preferred embodiment of the invention, a dose-response relationship is established based on quantification of the responses caused by a particular influence, representative of the underlying intracellular signalling process, using the methods described above and in examples 1-22 and 25. The dose-response relationship for the particular influence is then compared to the dose-response relationship obtained by performing the same assay in an instrument which allows parallel monitoring of all wells in a microtiter plate such as a FLIPR™ or an ordinary fluorescence plate reader for microtiter plates. If a good correlation between the dose-response relationships obtained from the two different measurement systems is obtained, it can be said that the parallel measurement mode has been validated (see examples 23 and 24). This implies that it can be used as the primary basis for a screening assay with the potential benefit of screening a significantly higher number of substances per unit of time for their influence on the response.

Imaging plate readers integrate the signal from each well into a single value per time point. Thus the data resulting from a single "run" of the instrument is a set of time series of single values, one for each well, with the injection of the test compound taking place at a known point in the time series. The primary advantage of this type of instrumentation is that it greatly increases the number of samples that can be processed in a given amount of time (the throughput). This is of great advantage when using the assay in a screening program for new pharmaceutical lead compounds.

The first step in the data analysis is to normalise the results from each well so that they can be compared with each other or with previously analysed known compounds. This always begins with correcting the signal by subtracting the instrument bias from all data points on a well-by-well basis. From this point, either of two techniques can be followed depending on the design of the assay:

Procedure 1: The average of the signal prior to the addition of the test compound is subtracted from all data points on a well-by-well basis.

Procedure 2: The data are corrected for any known background by subtracting the background value from all data points on a well-by-well basis. The resulting background-corrected data are normalised by dividing each data set by the average of the data values

prior to the injection of the test compound on a well-by-well basis.

The corrected or normalised time series data sets are then further reduced by a technique that converts the time series to a single value. There are at least three such approaches:

1. For transient responses, the maximum deviation from the baseline is determined. This is also known as the "peak height" technique.

2. Alternatively, the signal is integrated over time between pre-defined limits. If the data were treated according to Procedure 2 above, then the offset is subtracted such that the integral of a non-response is zero within the limit of measurement error. This is also known as the "peak area" technique.

3. If the response is a cumulative one, e.g., an exponential change to a new level, the result is taken as the either the difference or the ratio between the signal after a predetermined time and the signal prior to the addition of the test compound.

All of the above procedures reduce the data for a given well to one or more single values. For screening purposes, these values will be searched for those that are greater than a certain statistically determined cut-off value. For characterisation, the values represent a quantitative response, and are further treated in sets by techniques such as dose-response curve fitting.

In another embodiment of the invention, the measurement of redistribution is accomplished indirectly by taking advantage of the fact that in order for redistribution to occur, the probe will experience some change in its freedom, or restriction, of movement within the intracellular milieu. The degree of translocation will correlate with the amount of freely mobile luminophore in the cytoplasm. At a point in time after the test compound has begun to have any influence it may have, the amount or fraction of restricted luminophore can be measured by disrupting or permeabilising the plasma membrane of the cells and allowing the freely mobile luminophore to diffuse away. If the detection volume of the detector is limited to the region immediately surrounding the cells, and the overall volume into which the freely mobile luminophore can diffuse is much larger, then the freely mobile luminophore essentially disappears from the detector's view and its signal is

not recorded.

In one aspect of the invention, the above mentioned measurement of redistribution is made on cells with permanently permeabilised plasma membranes immersed in a solution mimicking the cytoplasmic environment. In this way the influence of compounds that can normally not enter the cytoplasm of cells can be tested.

The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

In one embodiment the biologically active polypeptide encoded by the nucleic acid

construct. In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, and 152 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a

patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a

peptide linker between “GeneX” and GFP in the resulting fusion protein.

Some of the steps involved in the development of a probe include the following:

- Identify the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.

- Design the gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if the gene is to be fused behind GFP, i.e. a GFP-”GeneX” fusion. If the gene is to be fused in front of GFP, i.e. a “GeneX”-GFP fusion, a stop codon must be avoided. Optionally, the full-length sequence of GeneX may not be used in the fusion, but merely the part that localizes and redistributes like GeneX in response to a signal. In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- Identify a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue

Collection (Virginia).

- Optimise the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg^{2+} and K^{+}, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

- Clone the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.

The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Once a DNA construct for a probe has been generated, its functionality and usefulness may

be evaluated by transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localisation.

The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localisation is an indication of whether the probe is likely to perform well. If it localises as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localised soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken up very many copies of the plasmid, and localisation will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localisation does not occur after prolonged time, it may be because the fusion to GFP has destroyed a localisation function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localisation, and no localisation is observed, it may be because the probe should not be localised at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterisation and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component

of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human gene product, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterisation and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions, then it's back to the drawing board.

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarisation and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribution has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method that will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm that takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not, can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

The final step is then to see whether there exists a possibility to increase the throughput of the assay to improve its utility as the basis of a screening program. In order to do this, a dose-response relationship is established based on quantification of the responses caused by a particular influence, representative of the underlying intracellular signalling process, using the methods described above and in examples 1-22 and 25. The dose-response relationship for the particular influence is then compared to the dose-response relationship obtained by performing the same assay in an instrument which allows parallel monitoring of all wells in a microtiter plate such as a FLIPR™ or an ordinary imaging or fluorescence plate reader for microtiter plates. If a good correlation between the dose-response relationships obtained from the two different measurement systems is obtained, it can be said that the parallel measurement mode has been validated (see examples 23 and 24). This implies that it can be used as the primary basis for a screening program with the potential

benefit of screening a significantly higher number of substances for their influence on the response per unit of time.

The process of developing an image-based assay is best illustrated by example. The development of such an assay for GLUT4 translocation is hereby described. GLUT4 is a member of the class of glucose transporter molecules that are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualise the glucôse uptake response non-invasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualised by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantify their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the

other artifacts. The result of this procedure is a binary image that shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

Another approach to the problem of quantifying GLUT 4 translocation has been performed and validated using the same type of experimental protocol but a different image processing approach. In this case the objects of interest in the cells are not the appearance of snircles at the plasma membrane but the disappearance of GLUT4-GFP fluorescence from its intracellular site. With this method the bright area, consisting of GLUT4-GFP, centrally located in each cell is identified by a thresholding procedure. This demarcates a certain area for the centrally located GLUT4-GFP. In the next step the total fluorescence intensity in this area is quantified on each image in the image series, i.e. over time. The response for each cell is defined as the difference in fluorescence intensity in the centrally located GLUT4-GFP area before and a fixed point in time after application of the influence. The dose-response relationship for insulin using the above described quantitation procedure is shown in Figure 13. It can be seen that the ED50 value for insulin to reduce central GLUT4-GFP fluorescence is 0.3 nM.

In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cells with substances which are known or suspected to exert an influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term “green fluorescent protein” is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie, M. *et al.* (1994) Science 263, 802-805)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed “modified GFP”. “GFP” as used herein includes wild-type

GFP derived from the jelly fish *Aequorea victoria* and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim *et al.* (1994). Proc.Natl.Acad.Sci. 91:26, pp 12501-12504, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from *Aequorea* Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the co-ordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases and cyclic nucleotide phosphodiesterases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance that has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, and chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not

experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

In the present context, the term "permeabilised living cell" is used to indicate cells where a pore forming agent such as Streptolysin O or *Staphylococcus Aureus* α-toxin has been applied and thereby incorporated into the plasma membrane in the cells. This creates proteinaceous pores with a defined pore size in the plasma membranes of the exposed cells. Pores could also be made by electroporation, i.e. exposing the cells to high voltage discharges, a procedure that creates small holes in the plasma membrane by coagulating integral membrane proteins. Treatment with a mild detergent such as saponin may accomplish the same thing. Common to all these treatments are that pores are formed only in the plasma membrane without affecting the integrity of cytoplasmic structural elements and organelles. The term living in this context means that the permeabilised cells bathed in a solution mimicking the intracellular milieu still have functional organelles, such as actively respiring mitochondria and endoplasmic reticulum that can take up and release calcium ions, and functional structural elements. The benefit of this method is that substances that normally can not traverse the plasma membrane, but most likely exert their influence intracellularly, can be introduced and their influence studied without cumbersome microinjection of the substances into single cells. Using this method the response to an influence can be recorded from many cells simultaneously.

In the present context, the term "permeabilisation" is intended to indicate the selective disruption of the plasma membrane barrier so that soluble substances freely mobile in the cytosol are lost from the cells. The permeabilisation can be achieved as described above under "permeabilised living cells" or by using other chemical detergents such as Triton X-100 or digitonin in carefully titrated amounts.

The term "physiologically relevant", when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

The terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered

arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived from a mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different cell types of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial), HLMVEC (human lung microvascular endothelial cells) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g.primary isolated human monocytes, macrophages, neutrophils, basophils, eosinophils and lyphocyte populations, AML-193, HL-60, RBL-1, adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at

least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKCα-GFP, PKCγ-GFP, and PKCε-GFP disclosed by Schmidt *et al.* and Sakai *et al.*, respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

The term "cyclic nucleotide phosphodiesterase" is intended to indicate an enzyme that is capable of inactivating the second messengers cAMP and cGMP by hydrolysis of their 3'-ester bond.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several amino acids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part

in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an intermediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample that has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may

substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments that serve to chemically cross-link and stabilise soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

In the present context a "screening assay" is intended to mean any measurement protocol, including materials, cells, instruments, chemicals, reagents, detection units, calibration and quantification procedures used to measure a response from mechanically intact or permeabilised living cells relevant to influences on an intracellular pathway.

The term "dose-response relationship" and "screening programme" is in the present context intended to mean a clear correlation between the quantified response of cells in a screening assay to application of an influence, such as a compound, and the concentration of the applied influence. The response to the influence may be both an up-regulation and a down-regulation of the quantified parameter used in the screening assay.

In the present context, the term "physiology" is intended to mean the normal function of biological and biochemical processes inside cells, between cells and in the whole organism or animal.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 μM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 μM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 μm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 μM forskolin (A), 50 μM forskolin (B), 1mM dbcAMP (C) and 100 μM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 μM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 μM forskolin and 100 μM IBMX (open arrow) followed by repeated washing with buffer containing 100 μM IBMX

(solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 μM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 μM forskolin, open arrow, to increase [cAMP]. N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 μm.

Figure 4. Dose-response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

Figure 5. Time from initiation of a response to half maximal ($t_{1/2max}$) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2max}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

Figure 6. Parallel dose-response analyses of forskolin induced cAMP elevation and PKAc-

F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on $[cAMP]_i$ was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCα-F64L-S65T-GFP fusion. Carbachol (100 μM added at 1.0 second) induced a transient redistribution of PKCα-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

Figure 8. BHK cells stably transfected with the hM1 receptor and PKCα-F64L-S65T-GFP fusion were treated with carbachol (1 μM, 10 μM, 100 μM). In single cells intracellular $[Ca^{2+}]$ was monitored simultaneously with the redistribution of PKCα-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca^{2+} concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the best regions for monitoring changes in the fluorescence intensity of the plasma membrane.

Figure 9.

a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 μM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.

c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.

d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

Figure 10.

a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 μm.

b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time. The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

Figure 13. Dose-response relationships for the influence of insulin on the disappearance of total fluorescence from the centrally located area of GLUT4-GFP. Data points indicate mean±SE.

Figure 14. Dose-response relationship for the translocation of PKCα-GFP in BHKhM1 cells stimulated with the muscarininc agonist carbamylcholine using a FLIPR™ to do the actual experiments.

Figure 15. Dose-response relationship for the translocation of PKAc-GFP in CHO/PKAc-F64L-S65T-GFP cells stimulated with forskolin using a FLIPR™ to do the actual experiments.

Figure 16. Dose-response relationship for the disappearance of fluorescence from permeabilised CHO/PKAc-F64L-S65T-GFP when previously exposed to different doses of forskolin.

EXAMPLES

EXAMPLE 1

Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways that lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G_s or G_i class.

The catalytic subunit of the murine cAMP dependent protein kinase (PKAc) was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

To construct the PKAc-F64L-S65T-GFP fusion, convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCgCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4) ,

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAgAACTTTTC (SEQ ID NO:1),

3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions:

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 μg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 μg penicillin-streptomycin mixture ml^{-1}, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells). Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 μg G418/ml (*Neo* marker) andPKAc-F64L-S65T-GFP was maintained with 500 μg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human α2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 μg penicillin-streptomycin mixture ml^{-1} and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were maintained at 37°C with a custom built stage heater.

Images were processed and analysed in the following manner:

Method 1: Stepwise procedure for quantitation of translocation of PKA:

1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).

2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).

3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.

4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.

5. The value determined in step 4 was subtracted from the image. All negative values were discarded.

6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.

7. Scintillation proximity assay (SPA) for independent quantitation of cAMP.

Method 2: Alternative method for quantitation of PKA redistribution:

1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.

2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.

3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.

Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca^{2+}-HEPES buffer including 100 μM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 μM forskolin (n=3), 10 μM forskolin (n=4) and 50 μM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).

Fig. 2 shows the progression of response in time following treatment with 1 μM forskolin.

Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 μM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behaviour of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 μM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin-induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10μM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased $[cAMP]_i$, cells were treated with a combination of 10 μM forskolin and 100 μM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 μM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localisation after removal of forskolin.

Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARα2a and the PKA-F64L-S65T-GFP probe were treated with 10 μM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 μM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G_i protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in $[cAMP]_i$ (Fig. 3H).

Fusion protein translocation correlated with $[cAMP]_i$

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose-dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose-response relationship was observed in the range from 0.01-50 μM forskolin (Fig. 6). A half-maximal stimulation was observed at about 2 μM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 μM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 μM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6).

EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5'mPKCα:
TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg
(SEQ ID NO:5),

3'mPKCα:
gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP:
TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAgAACTTTTC (SEQ ID NO:1),

3'F64L-S65T-GFP:
gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-XhoI casette as described in example 1.

BHK cells expressing the human M1 receptor under the control of the inducible metallothionine promoter and maintained with the dihydrofolate reductase marker were

transfected with the PKCα-F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 μg Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 μg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKCα-F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 μg Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 μg penicillin-streptomycin mixture ml^{-1} and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Method 1: Monitoring the PKCα activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKCα-F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKCα:

1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).

2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).

3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure – convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.

4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.

5. The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.

7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway that is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.

a) Construction of murine ERK1 - F64L-S65T-GFP fusion:

Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:

5'ERK1:
TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCTCCgggggg Cgggg (SEQ ID NO:7),

3'ERK1:
gTCATCTTCTCgAgTCTTTCAggCgCgCCCggggCCCTCTggCgCCCCTggCTgg (SEQ ID NO:8),

5'F64L-S65T-GFP:
TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAgAACTTTTC (SEQ ID NO:1)

3'F64L-S65T-GFP:
gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+XhoI.The two pairs of digested PCR products are subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10) . The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plamid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Redistribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4

Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway that is activated by e.g. many growth factors.

a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.

b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank

Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localisation of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5

Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway that is induced by some members of the TGFbeta family of cytokines.

a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26) . The PCR product was digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.

b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25) . The PCR product was digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto;

GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.

The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc chambers in DMEM with 10% FCS to 80% confluence and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

EXAMPLE 6

Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals that affect focal adhesions.

The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localised structures, identified as focal adhesion points (Fig. 11).

A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

EXAMPLE 7

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

The actin binding domain of the human alpha-actinin gene (GenBank Accession number:

X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin that caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

EXAMPLE 8

Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 & 47) under the control of a CMV promoter.

b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-

bottom/-stop (SEQ ID NO:15) . The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 & 65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. anisomycin.

EXAMPLE 9

Probes for detection of Jnk1 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19) . The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.

b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18) . The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank

Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

EXAMPLE 10

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83) . The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.

b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82) . The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution

from cytoplasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

EXAMPLE 11

Probes for detection of IkappaB kinase redistribution.

Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.

IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.

a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-IkappaB-kinase probe and/or the IkappaB-kinase-EGFP probe should achieve a more cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

EXAMPLE 12

Probes for detection of CDK2 redistribution.

Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds that modulate the activity of the pathway in living cells.

CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system that regulates the cell cycle.

a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.

b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

EXAMPLE 13

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitisation of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.

b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

EXAMPLE 14

Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.

b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution from cytoplasmic to membrane-associated within seconds in response to activation of the T cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

EXAMPLE 15

Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-

bottom/+stop (SEQ ID NO:23) . The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.

b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21) . The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

EXAMPLE 16

Probes for detection of protein-tyrosine phosphatase redistribution.

Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.

a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 & 117) under the control

of a CMV promoter.

b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 & 119) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

EXAMPLE 17

Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35) . The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 & 53) under the control of a CMV promoter.

b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using

PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 & 77) under the control of a CMV promoter.

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

EXAMPLE 18

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds that modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways that are induced by e.g. many cytokines and growth factors.

a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 & 55) under the control of a CMV promoter.

b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/-stop (SEQ ID NO:331). The PCR product was digested with restriction

enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78 & 79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

EXAMPLE 19

Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFAT, an activator of transcription, is a component of signalling pathways involved in e.g. immune responses.

a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 & 131) under the control of a CMV promoter.

b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/-stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 & 133) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

EXAMPLE 20

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways that are responsive to a varity of inducers including cytokines, lymphokines, and some immunosuppressive agents.

a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.

b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular

distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

EXAMPLE 21

Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA.

EXAMPLE 22

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of

which are activated by growth factors.

a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.

b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/-stop (SEQ ID NO:37) . The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

EXAMPLE 23

Measurement of the real-time redistribution of protein kinase C α isoform-GFP fusion (PKCα-GFP) in response to carbamylcholine stimulation of the muscarinic M1 receptor; 96 parallel redistribution measurements in microtiter plates.

BHK cells were stably expressing a recombinant human muscarinic typ 1 receptor, under the selection with 500 μg/ml Methotrexate, and also a PKCα-GFP construct (KaA 048), under the selection of 500 nM Zeocin. The cells were grown in 96-well plates (Packard ViewPlate, black with transparent bottom), washed and preincubated in a Hank's Buffered

Salt solution (HBSS) without phenol red, with 20 mM HEPES and 5.5 mM glucose.

The plate was measured in a FLIPR™ (Fluorescence Imaging Plate Reader) from Molecular Devices. The 488 nm emission line from an argon ion laser, run at between 0.4 and 0.8 W output, was used to excite fluorescence form the GFP. Emission wavelengths were collected through a 510 to 565 nm band pass filter.

The cells were challenged with three doses of carbamylcholine, an M1 receptor agonist known from previous studies to give a microscopically detectable redistribution of the PKCα-GFP construct [(Almholt *et al.* 1997)]. Measurements were made every 10 seconds for 5 minutes. After data handling including normalisation of baseline fluorescence for the different wells, background subtraction and averaging the 6 wells used for each concentration the data presented in figure 14 were obtained. It can clearly be seen (Fig 14) that carbamylcholine gave a time- and dose-dependent, and transient, decrease in fluorescence very similar to the time- and dose-dependent profile seen in microscopic fluorescence measurements [(see Almholt *et al.* 1997)]. This experiment was repeated twice on the same batch of cells with similar results.

EXAMPLE 24

Measurement of the real-time redistribution of cyclic-AMP dependent protein kinase catalytic subuit-GFP fusion (C-GFP^{LT}) in response to forskolin stimulation of the adenylate cyclase; 96 parallel redistribution measurements in microtiter plates.

CHO cells were stably transfected with hybrid DNA for the PKA catalytic subunit-F64L+S65T GFP (C-GFP^{LT}) fusion protein, and were typically under continuous selection with 1000 µg/ml zeocin (Invitrogen). The cells were grown without selection for 2 days in 96-well plates (Packard ViewPlate, black with transparent bottom), washed and preincubated in a Hank's Buffered Salt solution (HBSS) without phenol red, with 20 mM HEPES and 5.5 mM glucose.

The plate was measured in a FLIPR™ (Fluorescence Imaging Plate Reader) from Molecular Devices. The 488 nm emission line from an argon ion laser, run at between 0.4

and 0.8 W output, was used to excite fluorescence from the GFP. Emission wavelengths were collected through a 510 to 565 nm band pass filter.

The cells were challenged with three doses of forskolin (Fig 15), an adenylate cyclase agonist known from previous studies to give a microscopically detectable redistribution of the C-GFP^{LT} construct [(Almholt *et al.* 1998)]. Measurements were made every 10 seconds for over 6 minutes from the point of addition of forskolin. After data handling including normalisation of baseline fluorescence for the different wells, background subtraction and averaging the 6 wells used for each concentration the data presented below were obtained. It can clearly be seen in figure 15 that forskolin gave a time- and dose-dependent decrease in fluorescence very similar to the time- and dose-dependent profile seen in microscopic fluorescence measurements [(see Almholt *et al.* 1998)]. This experiment was repeated twice on the same batch of cells with similar results.

EXAMPLE 25

Measurement of the redistribution response of cyclic-AMP dependent protein kinase catalytic subuit-GFP fusion (C-GFP^{LT}) after forskolin stimulation of the adenylate cyclase; measurement of the change in total fluorescence upon permeabilisation of agonist-treated cells.

CHO cells were stably transfected with hybrid DNA for the PKA catalytic subunit-F64L+S65T GFP (C-GFP^{LT}) fusion protein, and were typically under continuous selection with 1000 μg/ml zeocin (Invitrogen). For the experiments reported here, cells were grown without selection to 90% confluence in 8-well tissue culture-treated Lab-Tek® chambered coverglass units (chambers, obtained from Nunc, Inc. Illinois, USA). Immediately prior to the experiment growth medium was washed from the cells and replaced with 200 μl HEPES buffer per well.

For the results reported here, chambers were measured using a cooled CCD camera (KAF1400 chip, Photometrics Ltd., USA) attached to an inverted microscope (Diaphot 300, Nikon, Japan) equipped with a x40 oil-immersion Fluar lens, NA 1.4. Cells were

illuminated with 450-490 nm light from a 50 W HBO lamp, and emitted light collected between 510-560 nm.

The cells were challenged with four doses of forskolin, an adenylate cyclase agonist known from previous studies to give a microscopically detectable redistribution of the C-GFP^{LT} construct [(Almholt *et al.* 1998)]. Images were collected at 10-second intervals for a period of 10 minutes for each treatment. Six minutes after the addition of forskolin or buffer control, Triton-X100 was added to a final concentration of 0.1%. The detergent releases freely mobile C-GFP^{LT} from the cells. The change in fluorescence resulting from this loss was measured after 1 minute of equilibration. After data handling including background subtraction and normalisation to pre-detergent values, the data presented in figure 16 were obtained. Permeabilisation caused decreases in fluorescence, the magnitude of which were dependent on the forskolin treatments. The dose-dependent profile for forskolin activation of the cAMP system as revealed by this method was very similar to that registered by other methods (see Almholt *et al.* 1998). This experiment was repeated twice on the same batch of cells with similar results.

EXAMPLE 26

Probe for detection of PKCbeta2 redistribution.

Useful for monitoring signalling pathways involving protein kinase C, e.g. for identifying compounds which modulate the activity of the pathway in living cells.

PKCbeta2, a serine/threonine protein kinase, is closely related to PKCalpha but not identical; it is a component of a signalling pathway that is activated by elevation of intracellular calcium concomitant with an increase in diacylglycerol species.

a) The human PKCbeta2 gene (GenBank Accession number: X07109) was amplified using PCR according to standard protocols with primers PKCbeta2-top (SEQ ID NO:162) and PKCbeta2-bottom (SEQ ID NO:163). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKCbeta2-

EGFP fusion (SEQ ID NO:146 & 147) under the control of a CMV promoter.

The resulting plasmids are transfected into BHK cells transfected with a human muscarinic acetylcholine receptor type M1. The cells are grown under standard conditions. The fluorescence of the cells is recorded as explained in example 3. Addition of 1μM -100μM carbachol causes a transient redistribution of fluorescence within the cells whereby it changes from a cytosolic location to the plasma membrane.

EXAMPLE 27

Probes for detection of PDE4D redistribution.

Useful for monitoring signalling pathways involving Protein Kinase A, e.g. to identify compounds which modulate the activity of the pathway in living cells.

PDE4D3, PDE4D4 and PDE4D5 are closely related splicing variants of PDE4D, a cAMP dependent phosphodiesterase. They are components of signalling pathways which involves cAMP.

The human PDE4D3, PDE4D4 and PDE4D5 genes (GenBank Accession numbers: L20970, L20969 and AF012073) are amplified using PCR according to standard protocols with the common bottom primer PDE4D-bottom (SEQ ID NO:159) and PDE4D3-top (SEQ ID NO:156), PDE4D4-top (SEQ ID NO:157) and PDE4D5-top respectively (SEQ ID NO:158) The PCR products are digested with restriction enzymes Hind3 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and EcoR1. This produces a PDE4D3-EGFP fusion (SEQ ID NO:154 & 155), a PDE4D4-EGFP fusion (SEQ ID NO:150 & 151) and a PDE4D5-EGFP fusion (SEQ ID NO:148 & 149), all three under the control of a CMV promoter.

The resulting plasmids are transfected into MVLEC cells. The cells are grown under standard conditions. The fluorescence of the cells is recorded as explained in example 3. Addition of test compounds may cause a redistribution of fluorescence within the cells from an organised cytosolic distribution to a more random one.

EXAMPLE 28

Probes for detection of PDE5 redistribution.

Useful for monitoring signalling pathways involving Protein Kinase G, e.g. to identify compounds which modulate the activity of the pathway in living cells.

PDE5 is a cGMP specific phosphodiesterase. It is a component of a signalling pathway which is activated by e.g. nitric oxide.

a) The human PDE5 gene (GenBank Accession numbers: AJ004865) is amplified using PCR according to standard protocols with primers PDE5-top (SEQ ID NO:160) and PDE5-bottom (SEQ ID NO:161). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a PDE5-EGFP fusion (SEQ ID NO 144 & 145) under the control of a CMV promoter.

The resulting plasmids are transfected into e.g. A10 cells. The cells are grown under standard conditions. The fluorescence of the cells is recorded as explained in example 3. Addition of test compounds may cause a redistribution of fluorescence within the cells from an organized cytosolic distribution to a more random one.

EXAMPLE 29

Probe for detection of Ikappa-kinase redistribution.

The human IKKbeta (GenBank Acc. No. AF031416) is amplified using PCR according to standard protocols with primers IKKbeta-top (SEQ ID NO:164) and IKKbeta-bottom (SEQ ID NO:165). The PCR product is digested with restriction enzymes Hind3 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and Acc65I. This produces a IKKbeta-EGFP fusion (SEQ ID NO 152 & 153) under the control of a CMV promoter.

EXAMPLE 30

Construction of catalytically inactive Erk1 probes.

A catalytically inactive probe has the advantage that it interferes less with the normal physiology of the cell while retaining its ability to report on activation of a cellular signalling pathway by redistribution.

The Erk1 probes described above in Example 3 were subjected to site specific mutagenesis which specifically replaced the lysine at amino acid residue number 71 in the native Erk1 sequence with arginine. This mutation is known to inactivate the catalytic activity of Erk1. The redistribution patterns of the inactive Erk1 probes were identical to the original Erk1 probes, i.e. they reported on activation of the pathway by redistributing from the cytoplasm into the nucleus. The establishment of stable cell lines expressing the probe was facilitated.

REFERENCES:

Adams, S.R., Harootunian, A.T., Buechler, Y.J., Taylor, S.S. & Tsien, R.Y. (1991) Nature **349**, 694-697.

Almholt, K., Arkhammar, P.O.G., Thastrup, O., & Tullin, S. (1997) Mol. Biology of the Cell **8**: Suppl. S: 72.

Almholt, K.,Terry, B.R., Skyggebjerg, O., Scudder, K., Tullin, S., Thastrup, O. (1998) [Manuscript], see Appendix II.

Barak, L.S., Ferguson, S.S.G., Zhang, J. & Caron, M.G. (1997) J. Biol. Chem. **272**:44, 27497-27500.

Bastiaens, P.I.H. & Jovin, T.M. (1996) Proc. Natl. Acad. Sci. USA **93**, 8407-8412.

Beals, C.R., Clipstone, N.A., Ho, S.N. & Crabtree, G.R. (1998) Genes and Development **11**:7, 824-834.

Blobe, G.C., Stribling, D.S., Fabbro, D., Stabel, S & Hannun, Y.A. (1996) J. Biol. Chem. **271**, 15823-15830.

Carey, K.L., Richards, S.A., Lounsbury, K.M. & Macara, I.G. (1996) J. Cell Biol. **133**: 5, 985-996.

Chalfie, M., Tu, Y., Euskirchen, G., Ward, W.W. & Prasher, D.C. (1994) Science **263**, 802-805.

Cossette, L.J., Hoglinger, O., Mou, L.J. & Shen, S.H. (1997) Exp. Cell Res. **223**, 459-466.

DeBernardi, M.A. & Brooker, G. (1996) Proc. Natl. Acad. Sci. USA **93**, 4577-4582.

Farese, R.V. (1992) Biochem. J. **288**, 319-323.

Fulop Jr., T., Leblanc, C., Lacombe, G. & Dupuis, G. (1995) FEBS Lett. **375**, 69-74.

Georget, V., Lobaccaro, J.M., Terouanne, B., Mangeat, P., Nicolas, J.C. & Sultan, C. (1997) Mol. Cell. Endocrinol. **129**:1, 17-26.

Godson, C., Masliah, E., Balboa, M.A., Ellisman, M.H. & Insel, P.A. (1996) Biochem. Biophys. Acta **1313**, 63-71.

Guiliano, K.A., DeBiasio, R, Dunlay, R.T., Gough, A., Volosky, J.M., Zock, J., Pavlakis, G.N. & Taylor, D.L. (1997) J. Biomol. Screening **2**:4, 249-259.

Khalil, R.A., Lajoie, C., Resnick, M.S. & Morgan, K.G. (1992) Am. J. Physiol. **263** (Cell Physiol. 32) C714-C719.

Oancea, E., Teruel, M.N., Quest, A.F.G. & Meyer, T. (1998) J. Cell Biol. **140**:3, 485-498.

Sano, M., Kohno, M. & Iwanaga, M. (1995) Brain Res. **688**, 213-218.

Sakai, N., Sasaki, K., Hasegawa, C., Ohkura, M., Sumioka, K., Shirai, Y. & Saito, N. (1996) Soc. Neuroscience 22, 69P (Abstract).

Sakai, N., Sakai, K. Hasegawa, C., Ohkura, M., Sumioka, K., Shirai, Y., & Naoaki, S. (1997) Japanese Journal of Pharmacology 73, 69P (Abstract of a meeting held 22-23 March).

Schmidt, D.J., Ikebe, M., Kitamura, K. & Fay, F.S. (1997) FASEB J. 11, 2924 (Abstract).

Schroeder, K. & Neagle, B.J. (1996) Biomolecular Screening 1, 75-80.

Silverman, L., Campbell, R. & Broach, J.R. (1998) Current Opinion in Chemical Biology 2:3, 397-403.

Stauffer, T.P., Ahn, S. & Meyer, T. (1998) Current Biol. 8:6, 343-346.

CLAIMS

1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on mechanically intact or permeabilised living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the luminescence characteristics to provide quantitative information correlating the recorded variation to the degree of the influence on the cellular response.

2. A method according to claim 1 for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact or permeabilised living cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information correlating the change in the measured property of the light to the degree of the influence on the intracellular pathway.

3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recorded variation according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.

4. A method according to any of claims 1-3, wherein the influence comprises contact between the mechanically intact or permeabilised living cells and a chemical substance and/or incubation of the mechanically intact or permeabilised living cells with a chemical substance.

5. A method according to any of claims 1-4, wherein the influence is a substance whose effect on an intracellular pathway is to be determined.

6. A method according to any of claims 1-5, wherein the cells comprise a group of cells contained within a spatial limitation.

7. A method according to any of claims 1-5, wherein the cells comprise multiple groups of cells contained within multiple spatial limitations.

8. A method according to any of claims 1-7, wherein the cells comprise multiple groups of cells that are qualitatively the same but are subjected to different influences.

9. A method according to any of claims 1-7, wherein the cells comprise multiple groups of cells that are qualitatively different but are subjected to the same influence.

10. A method according to any of claims 1-9, wherein the recording is performed by means of a detector capable of measuring total luminescence in a non-spatially resolved fashion, the recording comprising a time series of measurements of the total luminescence of the cells of one or several of the spatial limitations.

11. A method according to claim 10, wherein the signal is measured from individual spatial limitations one at a time, the recording being made in the individual spatial limitation by means of an apparatus to sequentially position each one of the limitations in the field of view of the detector, and repeating the positioning and measuring process until all of the spatial limitations have been measured.

12. A method according to claim 11, wherein the detector is a photomultiplier tube (PMT).

13. A method according to any of claims 1-9, wherein more than one of the spatial limitations are measured simultaneously.

14. A method according to claim 13, wherein the multiple spatial limitations are measured simultaneously by means of a one- or two-dimensional array detector, whereby the multiple spatial limitations are imaged onto the array detector such that discrete subsets of the detecting units (pixels) in the array detector measure the signal from one and

only one of the multiple spatial limitations, the signal from any one spatial limitation being the combined signal from those pixels that receive the image from one of the spatial limitations.

15. A method according to claim 14, wherein the detector is a linear diode array.

16. A method according to claim 14, wherein the detector is a video camera.

17. A method according to claim 14, wherein the detector is a charge transfer device.

18. A method according to claim 17, wherein the charge transfer device is a charge-coupled device.

19. A method according to any of claims 1-18, wherein the luminophore must be illuminated in order to emit light.

20. A method according to any of claims 13-18, wherein all of the multiple spatial limitations are simultaneously illuminated during the measurement operation.

21. A method according to any of claims 10-18, wherein the individual spatial limitations are singly illuminated only during the time period in which they are being measured.

22. A method according to any of claims 10-18, wherein the illumination is provided by a laser which is scanned in a raster fashion over some or all of the spatial limitations being measured, the scanning taking place at a rate substantially faster than the measurement process such that the illumination appears to the measurement process to be continuous in time and spatially uniform over the region being measured.

23. A method according to any of claims 1-22, wherein the spatial limitations are spatial limitations arranged in one or more arrays on a common carrier.

24. A method according to claim 23, wherein the spatial limitations are wells in a plate of microtiter type.

25. A method according to any of claims 1-22 wherein the spatial limitations are domains defined on a substrate on which the cells are present.

26. A method according to claim 25 wherein the domains are domains established by the presence of the cells on the substrate in a pattern defining the domains.

27. A method according to claim 25 wherein the domains are domains established by the spatial pattern of the influence as it is applied to or contacted with the cells.

28. A method according to any of claims 1-27, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

29. A method according to claim 28, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.

30. A method according to any of claims 1-29, wherein the cells are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

31. A method according to any of claims 1-30, wherein the luminophore is a luminophore that is capable of being redistributed in a manner that is physiologically relevant to the degree of the influence.

32. A method according to any of claims 1-30, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.

33. A method according to any of claims 1-30, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.

34. A method according to any of claims 1-30, wherein the luminophore is a luminophore

which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.

35. A method according to any of claims 1-30, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.

36. A method according to any of claims 1-30, wherein the variation in spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.

37. A method according to any of claims 1-35, wherein the intensity of the light being recorded is a function of the fluorescence lifetime, polarisation, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

38. A method according to any of claims 1-37, wherein the light to be measured passes through a filter which selects the desired component of the light to be measured and rejects other components.

39. A method according to any of claims 2-38, wherein the intracellular pathway is an intracellular signalling pathway.

40. A method according to any of claims 1-39, wherein the luminophore is a fluorophore.

41. A method according to any of claims 1-40, wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cells.

42. A method according to any of claims 1-41 for detecting intracellular redistribution of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising

a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

b) modulating the activity of the biologically active polypeptide by incubating the cells with a substance having biological activity, and

c) measuring the fluorescence produced by the incubated cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the redistribution of a biologically active polypeptide in said cells.

43. A method according to claim 42, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

44. A method according to claim 43, wherein the luminescent polypeptide is a GFP as defined herein.

45. A method according to claim 44, wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.

46. A method according to claim 45, wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.

47. A method according to claim 42, wherein the nucleotide sequence is a DNA sequence.

48. A method according to claims 42-47, wherein the modulation is activation.

49. A method according to claims 42-47, wherein the modulation is deactivation.

50. A method according to any of claims 1-49, wherein the cells are selected from the

group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.

51. A method according to claim 50, wherein the mechanically intact or permeabilised living cells are mammalian cells which, during the time period over which the influence is observed, are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

52. A method according to any of claims 1-51, wherein the mechanically intact or permeabilised living cells are part of a matrix of identical or non-identical cells.

53. A method according to any of claims 41-52, wherein the nucleotide sequence has been introduced into the cells in the form of a nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP.

54. A method according to claim 53, wherein the nucleic acid construct is a nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.

55. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 53 or 54, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

56. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 53 – 55, wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.

57. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 53, 54 or 56, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

58. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 53, 54 or 56, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.

59. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to any of claims 53-56, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.

60. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

61. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

62. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

63. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

64. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 63 which codes for a PKAc-F64L-S65T-GFP fusion.

65. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon

activation.

66. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

67. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

68. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 67, which codes for an ERK1-F64L-S65T-GFP fusion.

69. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 67, which codes for an EGFP-ERK1 fusion.

70. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 59, wherein the protein kinase is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

71. A method according to claim 53 or 54, wherein the nucleic acid construct is a nucleic acid construct according to claim 55 or 56, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

72. A method according to claim 53 -71, wherein the nucleic acid construct is a nucleic acid construct which is a DNA construct.

73. A method according to claim 53 –72, wherein the nucleic acid construct is a nucleic acid construct according to any of claims 53-72 wherein the gene encoding GFP is derived from Aequorea victoria.

74. A method according to claim 73, wherein the nucleic acid construct is a nucleic acid construct according to claim 73 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

75. A method according to claim 73, wherein the nucleic acid construct is a nucleic acid construct according to claim 73 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

76. A method according to claims 72 and 74, wherein the nucleic acid construct is a DNA construct according to claims 72 and 74 or, where applicable, 75, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, and 152 or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.

77. A method comprising a cell containing a nucleic acid construct according to any of claims 53-76 and capable of expressing the sequence encoded by the construct.

78. A method comprising a cell according to claim 77, which is a eukaryotic cell.

79. A method comprising a cell according to claim 77, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.

80. A method according to any of claims 1-79, as used in a screening program as defined herein.

81. A method according claim 80, wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling

pathway.

82. A method according to claim 80, wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

83. A method according to any of claims 1-82 wherein a fluorescent probe is used in back-tracking of signal transduction pathways as defined herein.

84. A method according to any of claims 1-83, for treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method.

85. A compound that modulates a component of an intracellular pathway as defined herein, as determined by any method according to any of claims 1-83.

86. A medical composition comprising a therapeutic amount of a compound identified according to any method according to any of claims 1-83.

87. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cells from said patient, transfecting the cells with at least one DNA sequence encoding a fluorescent probe according to any of the preceding claims, culturing the cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said

patient.

88. A method according to any of claims 1-83 of identifying a drug target among the group of biologically active polypeptides that are components of intracellular signalling pathways.

ABSTRACT

An improved method and tools for quantifying the effect of an influence on cellular response is described. In particular, an improved method is described for detecting intracellular translocation or redistribution of biologically active polypeptides. The invention also describes several ways of contacting the cells with a substance influencing a cellular response and extracting quantitative information relating to the response in a highly parallel fashion. The method may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process using commercially available parallel, high volume assay techniques, for example in connection with screening for new drugs, testing of substances for toxicity, and identifying drug targets for known or novel drugs.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT: NovoNordisk, BioImage

(ii) TITLE OF THE INVENTION: An Improved Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging

(iii) NUMBER OF SEQUENCES: 165

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: NovoNordisk, BioImage
(B) STREET: Mørkhøjbygade 28
(C) CITY: Søborg
(D) STATE: DK
(E) COUNTRY: DENMARK
(F) ZIP: 2860

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: , PV&P R
(B) REGISTRATION NUMBER:
(C) REFERENCE/DOCKET NUMBER:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTGGACACAA GCTTTGGACA CGGCGCGCCA TGAGTAAAGG AGAAGAACTT TTC 53

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GTCATCTTCT CGAGTCTTAC TCCTGAGGTT TGTATAGTTC ATCCATGCCA TGT 53

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGGCAACG CCGCCGCCGC CAAG 54

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GTCATCTTCT CGAGTCTTTC AGGCGCGCCC AAACTCAGTA AACTCCTTGC CACAC 55

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGCTGACG TTTACCCGGC CAACG 55

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GTCATCTTCT CGAGTCTTTC AGGCGCGCCC TACTGCACTT TGCAAGATTG GGTGC 55

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 64 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGCGGCGG CGGCGGCGGC TCCGGGGGGC 60
GGGG 64

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GTCATCTTCT CGAGTCTTTC AGGCGCGCCC GGGGCCCTCT GGCGCCCCTG GCTGG 55

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TAGAATTCAA CCATGGCGGC GGCGGCGGCG 30

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TAGGATCCCT AGGGGGCCTC CAGCACTCC 29

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TACTCGAGTA ACCATGGCGG CGGCGGCGGC G 31

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TAGGATCCAT AGATCTGTAT CCTGG 25

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TAGGATCCTT AAGATCTGTA TCCTGG 26

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

ATCTCGAGGG AAAATGTCTC AGGAGAGG 28

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGGATCCTC GGACTCCATC TCTTCTTG 28

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ATGGATCCTC AGGACTCCAT CTCTTCTTG 29

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTCTCGAGCC ATCATGAGCA GAAGCAAG 28

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GTGGATCCCA CTGCTGCACC TGTGCTA 27

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GTGGATCCTC ACTGCTGCAC CTGTGCTA 28

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC 40

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC 32

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:
(A) ORGANISM: p85-top-C

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GGGAGATCTA TGAGTGCTGA GGGGTACCAG 30

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC 34

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC 33

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GTGGTACCCA TGACATGCTT GAGCAACGCA C 31

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GTGGTACCTT ATGACATGCT TGAGCAACGC AC 32

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GTGAATTCGT CAATGGAGCT GGAAAACATC G 31

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GTGGATCCCT GCTGCTTCCG GTGGAGTTCG 30

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G 31

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GTAGATCTAC CATGGCGGGC TGGATCCAGG CC 32

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A 31

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G 31

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GTGAATTCAA CCATGGACAA TATGTCTATT ACG 33

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C 31

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC 32

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTCTCGAGGC ACCATGAGCG ACGTGGC 27

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TGGGATCCGA GGCCGTGCTG CTGGCCG 27

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1896 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1891
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCA ACC ATG GCG GCG GCG 768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ala Ala Ala
245 250 255

GCG GCT CAG GGG GGC GGG GGC GGG GAG CCC CGT AGA ACC GAG GGG GTC 816
Ala Ala Gln Gly Gly Gly Gly Gly Glu Pro Arg Arg Thr Glu Gly Val
260 265 270

GGC CCG GGG GTC CCG GGG GAG GTG GAG ATG GTG AAG GGG CAG CCG TTC 864
Gly Pro Gly Val Pro Gly Glu Val Glu Met Val Lys Gly Gln Pro Phe
275 280 285

GAC GTG GGC CCG CGC TAC ACG CAG TTG CAG TAC ATC GGC GAG GGC GCG 912
Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr Ile Gly Glu Gly Ala
290 295 300

TAC GGC ATG GTC AGC TCG GCC TAT GAC CAC GTG CGC AAG ACT CGC GTG 960
Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val Arg Lys Thr Arg Val
305 310 315 320

GCC ATC AAG AAG ATC AGC CCC TTC GAA CAT CAG ACC TAC TGC CAG CGC 1008
Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr Tyr Cys Gln Arg
325 330 335

ACG CTC CGG GAG ATC CAG ATC CTG CTG CGC TTC CGC CAT GAG AAT GTC 1056
Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe Arg His Glu Asn Val
340 345 350

ATC GGC ATC CGA GAC ATT CTG CGG GCG TCC ACC CTG GAA GCC ATG AGA 1104
Ile Gly Ile Arg Asp Ile Leu Arg Ala Ser Thr Leu Glu Ala Met Arg
355 360 365

GAT GTC TAC ATT GTG CAG GAC CTG ATG GAG ACT GAC CTG TAC AAG TTG 1152
Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp Leu Tyr Lys Leu
370 375 380

CTG AAA AGC CAG CAG CTG AGC AAT GAC CAT ATC TGC TAC TTC CTC TAC 1200
Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile Cys Tyr Phe Leu Tyr
385 390 395 400

CAG ATC CTG CGG GGC CTC AAG TAC ATC CAC TCC GCC AAC GTG CTC CAC 1248
Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu His

405 410 415

CGA GAT CTA AAG CCC TCC AAC CTG CTC AGC AAC ACC ACC TGC GAC CTT 1296
Arg Asp Leu Lys Pro Ser Asn Leu Leu Ser Asn Thr Thr Cys Asp Leu
420 425 430

AAG ATT TGT GAT TTC GGC CTG GCC CGG ATT GCC GAT CCT GAG CAT GAC 1344
Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala Asp Pro Glu His Asp
435 440 445

CAC ACC GGC TTC CTG ACG GAG TAT GTG GCT ACG CGC TGG TAC CGG GCC 1392
His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg Ala
450 455 460

CCA GAG ATC ATG CTG AAC TCC AAG GGC TAT ACC AAG TCC ATC GAC ATC 1440
Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp Ile
465 470 475 480

TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC TCT AAC CGG CCC ATC 1488
Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn Arg Pro Ile
485 490 495

TTC CCT GGC AAG CAC TAC CTG GAT CAG CTC AAC CAC ATT CTG GGC ATC 1536
Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly Ile
500 505 510

CTG GGC TCC CCA TCC CAG GAG GAC CTG AAT TGT ATC ATC AAC ATG AAG 1584
Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Met Lys
515 520 525

GCC CGA AAC TAC CTA CAG TCT CTG CCC TCC AAG ACC AAG GTG GCT TGG 1632
Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys Thr Lys Val Ala Trp
530 535 540

GCC AAG CTT TTC CCC AAG TCA GAC TCC AAA GCC CTT GAC CTG CTG GAC 1680
Ala Lys Leu Phe Pro Lys Ser Asp Ser Lys Ala Leu Asp Leu Leu Asp
545 550 555 560

CGG ATG TTA ACC TTT AAC CCC AAT AAA CGG ATC ACA GTG GAG GAA GCG 1728
Arg Met Leu Thr Phe Asn Pro Asn Lys Arg Ile Thr Val Glu Glu Ala
565 570 575

CTG GCT CAC CCC TAC CTG GAG CAG TAC TAT GAC CCG ACG GAT GAG CCA 1776
Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro Thr Asp Glu Pro
580 585 590

GTG GCC GAG GAG CCC TTC ACC TTC GCC ATG GAG CTG GAT GAC CTA CCT 1824
Val Ala Glu Glu Pro Phe Thr Phe Ala Met Glu Leu Asp Asp Leu Pro
595 600 605

AAG GAG CGG CTG AAG GAG CTC ATC TTC CAG GAG ACA GCA CGC TTC CAG 1872
Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu Thr Ala Arg Phe Gln
610 615 620

CCC GGA GTG CTG GAG GCC C CCTAG 1896
Pro Gly Val Leu Glu Ala Pro
625 630

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 631 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ala Ala Ala
                245                 250                 255
Ala Ala Gln Gly Gly Gly Gly Gly Glu Pro Arg Arg Thr Glu Gly Val
            260                 265                 270
Gly Pro Gly Val Pro Gly Glu Val Glu Met Val Lys Gly Gln Pro Phe
        275                 280                 285
Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr Ile Gly Glu Gly Ala
    290                 295                 300
Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val Arg Lys Thr Arg Val
305                 310                 315                 320
Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr Tyr Cys Gln Arg
                325                 330                 335
Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe Arg His Glu Asn Val
            340                 345                 350
```

Ile Gly Ile Arg Asp Ile Leu Arg Ala Ser Thr Leu Glu Ala Met Arg
355 360 365

Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp Leu Tyr Lys Leu
370 375 380

Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile Cys Tyr Phe Leu Tyr
385 390 395 400

Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu His
405 410 415

Arg Asp Leu Lys Pro Ser Asn Leu Leu Ser Asn Thr Thr Cys Asp Leu
420 425 430

Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala Asp Pro Glu His Asp
435 440 445

His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg Ala
450 455 460

Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp Ile
465 470 475 480

Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn Arg Pro Ile
485 490 495

Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly Ile
500 505 510

Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Met Lys
515 520 525

Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys Thr Lys Val Ala Trp
530 535 540

Ala Lys Leu Phe Pro Lys Ser Asp Ser Lys Ala Leu Asp Leu Leu Asp
545 550 555 560

Arg Met Leu Thr Phe Asn Pro Asn Lys Arg Ile Thr Val Glu Glu Ala
565 570 575

Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro Thr Asp Glu Pro
580 585 590

Val Ala Glu Glu Pro Phe Thr Phe Ala Met Glu Leu Asp Asp Leu Pro
595 600 605

Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu Thr Ala Arg Phe Gln
610 615 620

Pro Gly Val Leu Glu Ala Pro
625 630

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1818 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1815
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

```
GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC       96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC      144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC      192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG      240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG      288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG      336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC      384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC      432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC      480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC      528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC      576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG      624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC      672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC      720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GTA ACC ATG GCG GCG GCG GCG GCG GCG GGC CCG      768
Gly Leu Arg Ser Arg Val Thr Met Ala Ala Ala Ala Ala Ala Gly Pro
```

```
                        245                     250                     255

GAG ATG GTC CGC GGG CAG GTG TTC GAC GTG GGG CCG CGC TAC ACT AAT      816
Glu Met Val Arg Gly Gln Val Phe Asp Val Gly Pro Arg Tyr Thr Asn
                260                     265                     270

CTC TCG TAC ATC GGA GAA GGC GCC TAC GGC ATG GTT TGT TCT GCT TAT      864
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
            275                     280                     285

GAT AAT CTC AAC AAA GTT CGA GTT GCT ATC AAG AAA ATC AGT CCT TTT      912
Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
    290                     295                     300

GAG CAC CAG ACC TAC TGT CAG AGA ACC CTG AGA GAG ATA AAA ATC CTA      960
Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
305                     310                     315                     320

CTG CGC TTC AGA CAT GAG AAC ATC ATC GGC ATC AAT GAC ATC ATC CGG     1008
Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                325                     330                     335

GCA CCA ACC ATT GAG CAG ATG AAA GAT GTA TAT ATA GTA CAG GAC CTC     1056
Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
            340                     345                     350

ATG GAG ACA GAT CTT TAC AAG CTC TTG AAG ACA CAG CAC CTC AGC AAT     1104
Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
        355                     360                     365

GAT CAT ATC TGC TAT TTT CTT TAT CAG ATC CTG AGA GGA TTA AAG TAT     1152
Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
    370                     375                     380

ATA CAT TCA GCT AAT GTT CTG CAC CGT GAC CTC AAG CCT TCC AAC CTC     1200
Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
385                     390                     395                     400

CTG CTG AAC ACC ACT TGT GAT CTC AAG ATC TGT GAC TTT GGC CTT GCC     1248
Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
                405                     410                     415

CGT GTT GCA GAT CCA GAC CAT GAT CAT ACA GGG TTC TTG ACA GAG TAT     1296
Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
            420                     425                     430

GTA GCC ACG CGT TGG TAC AGA GCT CCA GAA ATT ATG TTG AAT TCC AAG     1344
Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
        435                     440                     445

GGT TAT ACC AAG TCC ATT GAT ATT TGG TCT GTG GGC TGC ATC CTG GCA     1392
Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
    450                     455                     460

GAG ATG CTA TCC AAC AGG CCT ATC TTC CCA GGA AAG CAT TAC CTT GAC     1440
Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
465                     470                     475                     480
```

CAG CTG AAT CAC ATC CTG GGT ATT CTT GGA TCT CCA TCA CAG GAA GAT 1488
Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
485 490 495

CTG AAT TGT ATA ATA AAT TTA AAA GCT AGA AAC TAT TTG CTT TCT CTC 1536
Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
500 505 510

CCG CAC AAA AAT AAG GTG CCG TGG AAC AGG TTG TTC CCA AAC GCT GAC 1584
Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
515 520 525

TCC AAA GCT CTG GAT TTA CTG GAT AAA ATG TTG ACA TTT AAC CCT CAC 1632
Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
530 535 540

AAG AGG ATT GAA GTT GAA CAG GCT CTG GCC CAC CCG TAC CTG GAG CAG 1680
Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
545 550 555 560

TAT TAT GAC CCA AGT GAT GAG CCC ATT GCT GAA GCA CCA TTC AAG TTT 1728
Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
565 570 575

GAC ATG GAG CTG GAC GAC TTA CCT AAG GAG AAG CTC AAA GAA CTC ATT 1776
Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
580 585 590

TTT GAA GAG ACT GCT CGA TTC CAG CCA GGA TAC AGA TCT TAA 1818
Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
595 600 605

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 605 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Val Thr Met Ala Ala Ala Ala Ala Ala Gly Pro
245 250 255
Glu Met Val Arg Gly Gln Val Phe Asp Val Gly Pro Arg Tyr Thr Asn
260 265 270
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
275 280 285
Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
290 295 300
Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
305 310 315 320
Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
325 330 335
Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
340 345 350
Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
355 360 365
Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
370 375 380
Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
385 390 395 400
Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
405 410 415
Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
420 425 430
Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
435 440 445
Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
450 455 460
Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
465 470 475 480
Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
485 490 495
Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
500 505 510
Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
515 520 525
Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
530 535 540
Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
545 550 555 560

Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
565 570 575

Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
580 585 590

Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
595 600 605

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2529 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2526
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

```
    130                 135                 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC      480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC      528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC      576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG      624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC      672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC      720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG TCA ATG GAG CTG GAA      768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Ser Met Glu Leu Glu
                245                 250                 255

AAC ATC GTG GCC AAC ACG GTC TTG CTG AAA GCC AGG GAA GGG GGC GGA      816
Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg Glu Gly Gly Gly
            260                 265                 270

GGA AAG CGC AAA GGG AAA AGC AAG AAG TGG AAA GAA ATC CTG AAG TTC      864
Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu Ile Leu Lys Phe
        275                 280                 285

CCT CAC ATT AGC CAG TGT GAA GAC CTC CGA AGG ACC ATA GAC AGA GAT      912
Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr Ile Asp Arg Asp
    290                 295                 300

TAC TGC AGT TTA TGT GAC AAG CAG CCA ATC GGG AGG CTG CTT TTC CGG      960
Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg Leu Leu Phe Arg
305                 310                 315                 320

CAG TTT TGT GAA ACC AGG CCT GGG CTG GAG TGT TAC ATT CAG TTC CTG     1008
Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr Ile Gln Phe Leu
                325                 330                 335

GAC TCC GTG GCA GAA TAT GAA GTT ACT CCA GAT GAA AAA CTG GGA GAG     1056
Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu Lys Leu Gly Glu
            340                 345                 350

AAA GGG AAG GAA ATT ATG ACC AAG TAC CTC ACC CCA AAG TCC CCT GTT     1104
Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro Lys Ser Pro Val
        355                 360                 365
```

TTC ATA GCC CAA GTT GGC CAA GAC CTG GTC TCC CAG ACG GAG GAG AAG 1152
Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln Thr Glu Glu Lys
370 375 380

CTC CTA CAG AAG CCG TGC AAA GAA CTC TTT TCT GCC TGT GCA CAG TCT 1200
Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala Cys Ala Gln Ser
385 390 395 400

GTC CAC GAG TAC CTG AGG GGA GAA CCA TTC CAC GAA TAT CTG GAC AGC 1248
Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu Tyr Leu Asp Ser
405 410 415

ATG TTT TTT GAC CGC TTT CTC CAG TGG AAG TGG TTG GAA AGG CAA CCG 1296
Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu Glu Arg Gln Pro
420 425 430

GTG ACC AAA AAC ACT TTC AGG CAG TAT CGA GTG CTA GGA AAA GGG GGC 1344
Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu Gly Lys Gly Gly
435 440 445

TTC GGG GAG GTC TGT GCC TGC CAG GTT CGG GCC ACG GGT AAA ATG TAT 1392
Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr Gly Lys Met Tyr
450 455 460

GCC TGC AAG CGC TTG GAG AAG AAG AGG ATC AAA AAG AGG AAA GGG GAG 1440
Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys Arg Lys Gly Glu
465 470 475 480

TCC ATG GCC CTC AAT GAG AAG CAG ATC CTC GAG AAG GTC AAC AGT CAG 1488
Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys Val Asn Ser Gln
485 490 495

TTT GTG GTC AAC CTG GCC TAT GCC TAC GAG ACC AAG GAT GCA CTG TGC 1536
Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys Asp Ala Leu Cys
500 505 510

TTG GTC CTG ACC ATC ATG AAT GGG GGT GAC CTG AAG TTC CAC ATC TAC 1584
Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys Phe His Ile Tyr
515 520 525

AAC ATG GGC AAC CCT GGC TTC GAG GAG GAG CGG GCC TTG TTT TAT GCG 1632
Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala Leu Phe Tyr Ala
530 535 540

GCA GAG ATC CTC TGC GGC TTA GAA GAC CTC CAC CGT GAG AAC ACC GTC 1680
Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg Glu Asn Thr Val
545 550 555 560

TAC CGA GAT CTG AAA CCT GAA AAC ATC CTG TTA GAT GAT TAT GGC CAC 1728
Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Asp Tyr Gly His
565 570 575

ATT AGG ATC TCA GAC CTG GGC TTG GCT GTG AAG ATC CCC GAG GGA GAC 1776
Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile Pro Glu Gly Asp
580 585 590

CTG ATC CGC GGC CGG GTG GGC ACT GTT GGC TAC ATG GCC CCC GAA GTC 1824
Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met Ala Pro Glu Val

```
        595                 600                 605

CTG AAC AAC CAG AGG TAC GGC CTG AGC CCC GAC TAC TGG GGC CTT GGC      1872
Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr Trp Gly Leu Gly
    610                 615                 620

TGC CTC ATC TAT GAG ATG ATC GAG GGC CAG TCG CCG TTC CGC GGC CGT      1920
Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro Phe Arg Gly Arg
625                 630                 635                 640

AAG GAG AAG GTG AAG CGG GAG GAG GTG GAC CGC CGG GTC CTG GAG ACG      1968
Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg Val Leu Glu Thr
                645                 650                 655

GAG GAG GTG TAC TCC CAC AAG TTC TCC GAG GAG GCC AAG TCC ATC TGC      2016
Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala Lys Ser Ile Cys
            660                 665                 670

AAG ATG CTG CTC ACG AAA GAT GCG AAG CAG AGG CTG GGC TGC CAG GAG      2064
Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu Gly Cys Gln Glu
        675                 680                 685

GAG GGG GCT GCA GAG GTC AAG AGA CAC CCC TTC TTC AGG AAC ATG AAC      2112
Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe Arg Asn Met Asn
    690                 695                 700

TTC AAG CGC TTA GAA GCC GGG ATG TTG GAC CCT CCC TTC GTT CCA GAC      2160
Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro Phe Val Pro Asp
705                 710                 715                 720

CCC CGC GCT GTG TAC TGT AAG GAC GTG CTG GAC ATC GAG CAG TTC TCC      2208
Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Glu Gln Phe Ser
                725                 730                 735

ACT GTG AAG GGC GTC AAT CTG GAC CAC ACA GAC GAC GAC TTC TAC TCC      2256
Thr Val Lys Gly Val Asn Leu Asp His Thr Asp Asp Asp Phe Tyr Ser
            740                 745                 750

AAG TTC TCC ACG GGC TCT GTG TCC ATC CCA TGG CAA AAC GAG ATG ATA      2304
Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln Asn Glu Met Ile
        755                 760                 765

GAA ACA GAA TGC TTT AAG GAG CTG AAC GTG TTT GGA CCT AAT GGT ACC      2352
Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly Pro Asn Gly Thr
    770                 775                 780

CTC CCG CCA GAT CTG AAC AGA AAC CAC CCT CCG GAA CCG CCC AAG AAA      2400
Leu Pro Pro Asp Leu Asn Arg Asn His Pro Pro Glu Pro Pro Lys Lys
785                 790                 795                 800

GGG CTG CTC CAG AGA CTC TTC AAG CGG CAG CAT CAG AAC AAT TCC AAG      2448
Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln Asn Asn Ser Lys
                805                 810                 815

AGT TCG CCC AGC TCC AAG ACC AGT TTT AAC CAC CAC ATA AAC TCA AAC      2496
Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His Ile Asn Ser Asn
            820                 825                 830
```

```
CAT GTC AGC TCG AAC TCC ACC GGA AGC AGC TAG                    2529
His Val Ser Ser Asn Ser Thr Gly Ser Ser
        835                 840
```

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 842 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Ser Met Glu Leu Glu
                245                 250                 255
Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg Glu Gly Gly Gly
            260                 265                 270
Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu Ile Leu Lys Phe
        275                 280                 285
Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr Ile Asp Arg Asp
    290                 295                 300
Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg Leu Leu Phe Arg
305                 310                 315                 320
```

Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr Ile Gln Phe Leu
325 330 335
Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu Lys Leu Gly Glu
340 345 350
Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro Lys Ser Pro Val
355 360 365
Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln Thr Glu Glu Lys
370 375 380
Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala Cys Ala Gln Ser
385 390 395 400
Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu Tyr Leu Asp Ser
405 410 415
Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu Glu Arg Gln Pro
420 425 430
Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu Gly Lys Gly Gly
435 440 445
Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr Gly Lys Met Tyr
450 455 460
Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys Arg Lys Gly Glu
465 470 475 480
Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys Val Asn Ser Gln
485 490 495
Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys Asp Ala Leu Cys
500 505 510
Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys Phe His Ile Tyr
515 520 525
Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala Leu Phe Tyr Ala
530 535 540
Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg Glu Asn Thr Val
545 550 555 560
Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Asp Tyr Gly His
565 570 575
Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile Pro Glu Gly Asp
580 585 590
Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met Ala Pro Glu Val
595 600 605
Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr Trp Gly Leu Gly
610 615 620
Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro Phe Arg Gly Arg
625 630 635 640
Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg Val Leu Glu Thr
645 650 655
Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala Lys Ser Ile Cys
660 665 670
Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu Gly Cys Gln Glu
675 680 685
Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe Arg Asn Met Asn
690 695 700
Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro Phe Val Pro Asp
705 710 715 720
Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Glu Gln Phe Ser
725 730 735
Thr Val Lys Gly Val Asn Leu Asp His Thr Asp Asp Asp Phe Tyr Ser
740 745 750
Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln Asn Glu Met Ile
755 760 765
Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly Pro Asn Gly Thr
770 775 780

Leu Pro Pro Asp Leu Asn Arg Asn His Pro Pro Glu Pro Pro Lys Lys
785 790 795 800
Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln Asn Asn Ser Lys
805 810 815
Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His Ile Asn Ser Asn
820 825 830
His Val Ser Ser Asn Ser Thr Gly Ser Ser
835 840

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1902 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1899
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

```
ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC     432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC     480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC     528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC     576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG     624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC     672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC     720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GCT CGA GCC ATC ATG AGC AGA AGC AAG CGT GAC     768
Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp
                245                 250                 255

AAC AAT TTT TAT AGT GTA GAG ATT GGA GAT TCT ACA TTC ACA GTC CTG     816
Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
            260                 265                 270

AAA CGA TAT CAG AAT TTA AAA CCT ATA GGC TCA GGA GCT CAA GGA ATA     864
Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
        275                 280                 285

GTA TGC GCA GCT TAT GAT GCC ATT CTT GAA AGA AAT GTT GCA ATC AAG     912
Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
    290                 295                 300

AAG CTA AGC CGA CCA TTT CAG AAT CAG ACT CAT GCC AAG CGG GCC TAC     960
Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
305                 310                 315                 320

AGA GAG CTA GTT CTT ATG AAA TGT GTT AAT CAC AAA AAT ATA ATT GGC    1008
Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
                325                 330                 335

CTT TTG AAT GTT TTC ACA CCA CAG AAA TCC CTA GAA GAA TTT CAA GAT    1056
Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
            340                 345                 350

GTT TAC ATA GTC ATG GAG CTC ATG GAT GCA AAT CTT TGC CAA GTG ATT    1104
Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
```

355 360 365

CAG ATG GAG CTA GAT CAT GAA AGA ATG TCC TAC CTT CTC TAT CAG ATG 1152
Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
370 375 380

CTG TGT GGA ATC AAG CAC CTT CAT TCT GCT GGA ATT ATT CAT CGG GAC 1200
Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
385 390 395 400

TTA AAG CCC AGT AAT ATA GTA GTA AAA TCT GAT TGC ACT TTG AAG ATT 1248
Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
405 410 415

CTT GAC TTC GGT CTG GCC AGG ACT GCA GGA ACG AGT TTT ATG ATG ACG 1296
Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
420 425 430

CCT TAT GTA GTG ACT CGC TAC TAC AGA GCA CCC GAG GTC ATC CTT GGC 1344
Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
435 440 445

ATG GGC TAC AAG GAA AAC GTG GAT TTA TGG TCT GTG GGG TGC ATT ATG 1392
Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
450 455 460

GGA GAA ATG GTT TGC CAC AAA ATC CTC TTT CCA GGA AGG GAC TAT ATT 1440
Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
465 470 475 480

GAT CAG TGG AAT AAA GTT ATT GAA CAG CTT GGA ACA CCA TGT CCT GAA 1488
Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
485 490 495

TTC ATG AAG AAA CTG CAA CCA ACA GTA AGG ACT TAC GTT GAA AAC AGA 1536
Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
500 505 510

CCT AAA TAT GCT GGA TAT AGC TTT GAG AAA CTC TTC CCT GAT GTC CTT 1584
Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
515 520 525

TTC CCA GCT GAC TCA GAA CAC AAC AAA CTT AAA GCC AGT CAG GCA AGG 1632
Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
530 535 540

GAT TTG TTA TCC AAA ATG CTG GTA ATA GAT GCA TCT AAA AGG ATC TCT 1680
Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
545 550 555 560

GTA GAT GAA GCT CTC CAA CAC CCG TAC ATC AAT GTC TGG TAT GAT CCT 1728
Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
565 570 575

TCT GAA GCA GAA GCT CCA CCA CCA AAG ATC CCT GAC AAG CAG TTA GAT 1776
Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
580 585 590

GAA AGG GAA CAC ACA ATA GAA GAG TGG AAA GAA TTG ATA TAT AAG GAA 1824
Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
595 600 605

GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872
Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
610 615 620

CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902
Pro Ser Pro Leu Ala Gln Val Gln Gln
625 630

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 633 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp
245 250 255

```
Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
            260                 265                 270
Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
        275                 280                 285
Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
    290                 295                 300
Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
305                 310                 315                 320
Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
                325                 330                 335
Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
            340                 345                 350
Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
        355                 360                 365
Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
    370                 375                 380
Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
385                 390                 395                 400
Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
                405                 410                 415
Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
            420                 425                 430
Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
        435                 440                 445
Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
    450                 455                 460
Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
465                 470                 475                 480
Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
                485                 490                 495
Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
            500                 505                 510
Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
        515                 520                 525
Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
    530                 535                 540
Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
545                 550                 555                 560
Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
                565                 570                 575
Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
            580                 585                 590
Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
        595                 600                 605
Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
    610                 615                 620
Pro Ser Pro Leu Ala Gln Val Gln Gln
625                 630
```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 1824 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1821
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu

```
        195                     200                     205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC      672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC      720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GGG AAA ATG TCT CAG GAG AGG CCC ACG TTC TAC      768
Gly Leu Arg Ser Arg Gly Lys Met Ser Gln Glu Arg Pro Thr Phe Tyr
                245                 250                 255

CGG CAG GAG CTG AAC AAG ACA ATC TGG GAG GTG CCC GAG CGT TAC CAG      816
Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln
            260                 265                 270

AAC CTG TCT CCA GTG GGC TCT GGC GCC TAT GGC TCT GTG TGT GCT GCT      864
Asn Leu Ser Pro Val Gly Ser Gly Ala Tyr Gly Ser Val Cys Ala Ala
        275                 280                 285

TTT GAC ACA AAA ACG GGG TTA CGT GTG GCA GTG AAG AAG CTC TCC AGA      912
Phe Asp Thr Lys Thr Gly Leu Arg Val Ala Val Lys Lys Leu Ser Arg
    290                 295                 300

CCA TTT CAG TCC ATC ATT CAT GCG AAA AGA ACC TAC AGA GAA CTG CGG      960
Pro Phe Gln Ser Ile Ile His Ala Lys Arg Thr Tyr Arg Glu Leu Arg
305                 310                 315                 320

TTA CTT AAA CAT ATG AAA CAT GAA AAT GTG ATT GGT CTG TTG GAC GTT     1008
Leu Leu Lys His Met Lys His Glu Asn Val Ile Gly Leu Leu Asp Val
                325                 330                 335

TTT ACA CCT GCA AGG TCT CTG GAG GAA TTC AAT GAT GTG TAT CTG GTG     1056
Phe Thr Pro Ala Arg Ser Leu Glu Glu Phe Asn Asp Val Tyr Leu Val
            340                 345                 350

ACC CAT CTC ATG GGG GCA GAT CTG AAC AAC ATT GTG AAA TGT CAG AAG     1104
Thr His Leu Met Gly Ala Asp Leu Asn Asn Ile Val Lys Cys Gln Lys
        355                 360                 365

CTT ACA GAT GAC CAT GTT CAG TTC CTT ATC TAC CAA ATT CTC CGA GGT     1152
Leu Thr Asp Asp His Val Gln Phe Leu Ile Tyr Gln Ile Leu Arg Gly
    370                 375                 380

CTA AAG TAT ATA CAT TCA GCT GAC ATA ATT CAC AGG GAC CTA AAA CCT     1200
Leu Lys Tyr Ile His Ser Ala Asp Ile Ile His Arg Asp Leu Lys Pro
385                 390                 395                 400

AGT AAT CTA GCT GTG AAT GAA GAC TGT GAG CTG AAG ATT CTG GAT TTT     1248
Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys Ile Leu Asp Phe
                405                 410                 415

GGA CTG GCT CGG CAC ACA GAT GAT GAA ATG ACA GGC TAC GTG GCC ACT     1296
Gly Leu Ala Arg His Thr Asp Asp Glu Met Thr Gly Tyr Val Ala Thr
            420                 425                 430
```

AGG TGG TAC AGG GCT CCT GAG ATC ATG CTG AAC TGG ATG CAT TAC AAC 1344
Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn
435 440 445

CAG ACA GTT GAT ATT TGG TCA GTG GGA TGC ATA ATG GCC GAG CTG TTG 1392
Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu
450 455 460

ACT GGA AGA ACA TTG TTT CCT GGT ACA GAC CAT ATT GAT CAG TTG AAG 1440
Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys
465 470 475 480

CTC ATT TTA AGA CTC GTT GGA ACC CCA GGG GCT GAG CTT TTG AAG AAA 1488
Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys
485 490 495

ATC TCC TCA GAG TCT GCA AGA AAC TAT ATT CAG TCT TTG ACT CAG ATG 1536
Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met
500 505 510

CCG AAG ATG AAC TTT GCG AAT GTA TTT ATT GGT GCC AAT CCC CTG GCT 1584
Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala
515 520 525

GTC GAC TTG CTG GAG AAG ATG CTT GTA TTG GAC TCA GAT AAG AGA ATT 1632
Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile
530 535 540

ACA GCG GCC CAA GCC CTT GCA CAT GCC TAC TTT GCT CAG TAC CAC GAT 1680
Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp
545 550 555 560

CCT GAT GAT GAA CCA GTG GCC GAT CCT TAT GAT CAG TCC TTT GAA AGC 1728
Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser
565 570 575

AGG GAC CTC CTT ATA GAT GAG TGG AAA AGC CTG ACC TAT GAT GAA GTC 1776
Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val
580 585 590

ATC AGC TTT GTG CCA CCA CCC CTT GAC CAA GAA GAG ATG GAG TCC TGA 1824
Ile Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser
595 600 605

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 607 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Gly Lys Met Ser Gln Glu Arg Pro Thr Phe Tyr
245 250 255
Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln
260 265 270
Asn Leu Ser Pro Val Gly Ser Gly Ala Tyr Gly Ser Val Cys Ala Ala
275 280 285
Phe Asp Thr Lys Thr Gly Leu Arg Val Ala Val Lys Lys Leu Ser Arg
290 295 300
Pro Phe Gln Ser Ile Ile His Ala Lys Arg Thr Tyr Arg Glu Leu Arg
305 310 315 320
Leu Leu Lys His Met Lys His Glu Asn Val Ile Gly Leu Leu Asp Val
325 330 335
Phe Thr Pro Ala Arg Ser Leu Glu Glu Phe Asn Asp Val Tyr Leu Val
340 345 350
Thr His Leu Met Gly Ala Asp Leu Asn Asn Ile Val Lys Cys Gln Lys
355 360 365
Leu Thr Asp Asp His Val Gln Phe Leu Ile Tyr Gln Ile Leu Arg Gly
370 375 380
Leu Lys Tyr Ile His Ser Ala Asp Ile Ile His Arg Asp Leu Lys Pro
385 390 395 400
Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys Ile Leu Asp Phe
405 410 415
Gly Leu Ala Arg His Thr Asp Asp Glu Met Thr Gly Tyr Val Ala Thr
420 425 430
Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn
435 440 445
Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu
450 455 460

Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys
465 470 475 480
Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys
485 490 495
Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met
500 505 510
Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala
515 520 525
Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile
530 535 540
Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp
545 550 555 560
Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser
565 570 575
Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val
580 585 590
Ile Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Glu Met Glu Ser
595 600 605

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2907 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2904
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu

85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT ATG AGT GCT GAG GGG TAC CAG TAC AGA GCG CTG TAT 768
Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr
245 250 255

GAT TAT AAA AAG GAA AGA GAA GAA GAT ATT GAC TTG CAC TTG GGT GAC 816
Asp Tyr Lys Lys Glu Arg Glu Glu Asp Ile Asp Leu His Leu Gly Asp
260 265 270

ATA TTG ACT GTG AAT AAA GGG TCC TTA GTA GCT CTT GGA TTC AGT GAT 864
Ile Leu Thr Val Asn Lys Gly Ser Leu Val Ala Leu Gly Phe Ser Asp
275 280 285

GGA CAG GAA GCC AGG CCT GAA GAA ATT GGC TGG TTA AAT GGC TAT AAT 912
Gly Gln Glu Ala Arg Pro Glu Glu Ile Gly Trp Leu Asn Gly Tyr Asn
290 295 300

GAA ACC ACA GGG GAA AGG GGG GAC TTT CCG GGA ACT TAC GTA GAA TAT 960
Glu Thr Thr Gly Glu Arg Gly Asp Phe Pro Gly Thr Tyr Val Glu Tyr
305 310 315 320

```
ATT GGA AGG AAA AAA ATC TCG CCT CCC ACA CCA AAG CCC CGG CCA CCT    1008
Ile Gly Arg Lys Lys Ile Ser Pro Pro Thr Pro Lys Pro Arg Pro Pro
                325                 330                 335

CGG CCT CTT CCT GTT GCA CCA GGT TCT TCG AAA ACT GAA GCA GAT GTT    1056
Arg Pro Leu Pro Val Ala Pro Gly Ser Ser Lys Thr Glu Ala Asp Val
            340                 345                 350

GAA CAA CAA GCT TTG ACT CTC CCG GAT CTT GCA GAG CAG TTT GCC CCT    1104
Glu Gln Gln Ala Leu Thr Leu Pro Asp Leu Ala Glu Gln Phe Ala Pro
        355                 360                 365

CCT GAC ATT GCC CCG CCT CTT CTT ATC AAG CTC GTG GAA GCC ATT GAA    1152
Pro Asp Ile Ala Pro Pro Leu Leu Ile Lys Leu Val Glu Ala Ile Glu
    370                 375                 380

AAG AAA GGT CTG GAA TGT TCA ACT CTA TAC AGA ACA CAG AGC TCC AGC    1200
Lys Lys Gly Leu Glu Cys Ser Thr Leu Tyr Arg Thr Gln Ser Ser Ser
385                 390                 395                 400

AAC CTG GCA GAA TTA CGA CAG CTT CTT GAT TGT GAT ACA CCC TCC GTG    1248
Asn Leu Ala Glu Leu Arg Gln Leu Leu Asp Cys Asp Thr Pro Ser Val
                405                 410                 415

GAC TTG GAA ATG ATC GAT GTG CAC GTT TTG GCT GAC GCT TTC AAA CGC    1296
Asp Leu Glu Met Ile Asp Val His Val Leu Ala Asp Ala Phe Lys Arg
            420                 425                 430

TAT CTC CTG GAC TTA CCA AAT CCT GTC ATT CCA GCA GCC GTT TAC AGT    1344
Tyr Leu Leu Asp Leu Pro Asn Pro Val Ile Pro Ala Ala Val Tyr Ser
        435                 440                 445

GAA ATG ATT TCT TTA GCT CCA GAA GTA CAA AGC TCC GAA GAA TAT ATT    1392
Glu Met Ile Ser Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile
    450                 455                 460

CAG CTA TTG AAG AAG CTT ATT AGG TCG CCT AGC ATA CCT CAT CAG TAT    1440
Gln Leu Leu Lys Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr
465                 470                 475                 480

TGG CTT ACG CTT CAG TAT TTG TTA AAA CAT TTC TTC AAG CTC TCT CAA    1488
Trp Leu Thr Leu Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln
                485                 490                 495

ACC TCC AGC AAA AAT CTG TTG AAT GCA AGA GTA CTC TCT GAA ATT TTC    1536
Thr Ser Ser Lys Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe
            500                 505                 510

AGC CCT ATG CTT TTC AGA TTC TCA GCA GCC AGC TCT GAT AAT ACT GAA    1584
Ser Pro Met Leu Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu
        515                 520                 525

AAC CTC ATA AAA GTT ATA GAA ATT TTA ATC TCA ACT GAA TGG AAT GAA    1632
Asn Leu Ile Lys Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu
    530                 535                 540

CGA CAG CCT GCA CCA GCA CTG CCT CCT AAA CCA CCA AAA CCT ACT ACT    1680
Arg Gln Pro Ala Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr
```

545 550 555 560

GTA GCC AAC AAC GGT ATG AAT AAC AAT ATG TCC TTA CAA AAT GCT GAA 1728
Val Ala Asn Asn Gly Met Asn Asn Asn Met Ser Leu Gln Asn Ala Glu
565 570 575

TGG TAC TGG GGA GAT ATC TCG AGG GAA GAA GTG AAT GAA AAA CTT CGA 1776
Trp Tyr Trp Gly Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg
580 585 590

GAT ACA GCA GAC GGG ACC TTT TTG GTA CGA GAT GCG TCT ACT AAA ATG 1824
Asp Thr Ala Asp Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met
595 600 605

CAT GGT GAT TAT ACT CTT ACA CTA AGG AAA GGG GGA AAT AAC AAA TTA 1872
His Gly Asp Tyr Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu
610 615 620

ATC AAA ATA TTT CAT CGA GAT GGG AAA TAT GGC TTC TCT GAC CCA TTA 1920
Ile Lys Ile Phe His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu
625 630 635 640

ACC TTC AGT TCT GTG GTT GAA TTA ATA AAC CAC TAC CGG AAT GAA TCT 1968
Thr Phe Ser Ser Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser
645 650 655

CTA GCT CAG TAT AAT CCC AAA TTG GAT GTG AAA TTA CTT TAT CCA GTA 2016
Leu Ala Gln Tyr Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val
660 665 670

TCC AAA TAC CAA CAG GAT CAA GTT GTC AAA GAA GAT AAT ATT GAA GCT 2064
Ser Lys Tyr Gln Gln Asp Gln Val Val Lys Glu Asp Asn Ile Glu Ala
675 680 685

GTA GGG AAA AAA TTA CAT GAA TAT AAC ACT CAG TTT CAA GAA AAA AGT 2112
Val Gly Lys Lys Leu His Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser
690 695 700

CGA GAA TAT GAT AGA TTA TAT GAA GAA TAT ACC CGC ACA TCC CAG GAA 2160
Arg Glu Tyr Asp Arg Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu
705 710 715 720

ATC CAA ATG AAA AGG ACA GCT ATT GAA GCA TTT AAT GAA ACC ATA AAA 2208
Ile Gln Met Lys Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys
725 730 735

ATA TTT GAA GAA CAG TGC CAG ACC CAA GAG CGG TAC AGC AAA GAA TAC 2256
Ile Phe Glu Glu Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr
740 745 750

ATA GAA AAG TTT AAA CGT GAA GGC AAT GAG AAA GAA ATA CAA AGG ATT 2304
Ile Glu Lys Phe Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile
755 760 765

ATG CAT AAT TAT GAT AAG TTG AAG TCT CGA ATC AGT GAA ATT ATT GAC 2352
Met His Asn Tyr Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp
770 775 780

AGT AGA AGA AGA TTG GAA GAA GAC TTG AAG AAG CAG GCA GCT GAG TAT 2400
Ser Arg Arg Arg Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu Tyr
785 790 795 800

CGA GAA ATT GAC AAA CGT ATG AAC AGC ATT AAA CCA GAC CTT ATC CAG 2448
Arg Glu Ile Asp Lys Arg Met Asn Ser Ile Lys Pro Asp Leu Ile Gln
805 810 815

CTG AGA AAG ACG AGA GAC CAA TAC TTG ATG TGG TTG ACT CAA AAA GGT 2496
Leu Arg Lys Thr Arg Asp Gln Tyr Leu Met Trp Leu Thr Gln Lys Gly
820 825 830

GTT CGG CAA AAG AAG TTG AAC GAG TGG TTG GGC AAT GAA AAC ACT GAA 2544
Val Arg Gln Lys Lys Leu Asn Glu Trp Leu Gly Asn Glu Asn Thr Glu
835 840 845

GAC CAA TAT TCA CTG GTG GAA GAT GAT GAA GAT TTG CCC CAT CAT GAT 2592
Asp Gln Tyr Ser Leu Val Glu Asp Asp Glu Asp Leu Pro His His Asp
850 855 860

GAG AAG ACA TGG AAT GTT GGA AGC AGC AAC CGA AAC AAA GCT GAA AAC 2640
Glu Lys Thr Trp Asn Val Gly Ser Ser Asn Arg Asn Lys Ala Glu Asn
865 870 875 880

CTG TTG CGA GGG AAG CGA GAT GGC ACT TTT CTT GTC CGG GAG AGC AGT 2688
Leu Leu Arg Gly Lys Arg Asp Gly Thr Phe Leu Val Arg Glu Ser Ser
885 890 895

AAA CAG GGC TGC TAT GCC TGC TCT GTA GTG GTG GAC GGC GAA GTA AAG 2736
Lys Gln Gly Cys Tyr Ala Cys Ser Val Val Val Asp Gly Glu Val Lys
900 905 910

CAT TGT GTC ATA AAC AAA ACA GCA ACT GGC TAT GGC TTT GCC GAG CCC 2784
His Cys Val Ile Asn Lys Thr Ala Thr Gly Tyr Gly Phe Ala Glu Pro
915 920 925

TAT AAC TTG TAC AGC TCT CTG AAA GAA CTG GTG CTA CAT TAC CAA CAC 2832
Tyr Asn Leu Tyr Ser Ser Leu Lys Glu Leu Val Leu His Tyr Gln His
930 935 940

ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC 2880
Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr
945 950 955 960

CCA GTA TAT GCA CAG CAG AGG CGA TGA 2907
Pro Val Tyr Ala Gln Gln Arg Arg
965

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 968 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr
                245                 250                 255
Asp Tyr Lys Lys Glu Arg Glu Glu Asp Ile Asp Leu His Leu Gly Asp
            260                 265                 270
Ile Leu Thr Val Asn Lys Gly Ser Leu Val Ala Leu Gly Phe Ser Asp
        275                 280                 285
Gly Gln Glu Ala Arg Pro Glu Glu Ile Gly Trp Leu Asn Gly Tyr Asn
    290                 295                 300
Glu Thr Thr Gly Glu Arg Gly Asp Phe Pro Gly Thr Tyr Val Glu Tyr
305                 310                 315                 320
Ile Gly Arg Lys Lys Ile Ser Pro Pro Thr Pro Lys Pro Arg Pro Pro
                325                 330                 335
Arg Pro Leu Pro Val Ala Pro Gly Ser Ser Lys Thr Glu Ala Asp Val
            340                 345                 350
Glu Gln Gln Ala Leu Thr Leu Pro Asp Leu Ala Glu Gln Phe Ala Pro
        355                 360                 365
Pro Asp Ile Ala Pro Pro Leu Leu Ile Lys Leu Val Glu Ala Ile Glu
    370                 375                 380
Lys Lys Gly Leu Glu Cys Ser Thr Leu Tyr Arg Thr Gln Ser Ser Ser
385                 390                 395                 400
Asn Leu Ala Glu Leu Arg Gln Leu Leu Asp Cys Asp Thr Pro Ser Val
                405                 410                 415
Asp Leu Glu Met Ile Asp Val His Val Leu Ala Asp Ala Phe Lys Arg
            420                 425                 430
```

Tyr Leu Leu Asp Leu Pro Asn Pro Val Ile Pro Ala Ala Val Tyr Ser
        435   440   445
Glu Met Ile Ser Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile
    450   455   460
Gln Leu Leu Lys Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr
465   470   475   480
Trp Leu Thr Leu Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln
                485   490   495
Thr Ser Ser Lys Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe
            500   505   510
Ser Pro Met Leu Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu
        515   520   525
Asn Leu Ile Lys Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu
    530   535   540
Arg Gln Pro Ala Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr
545   550   555   560
Val Ala Asn Asn Gly Met Asn Asn Asn Met Ser Leu Gln Asn Ala Glu
                565   570   575
Trp Tyr Trp Gly Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg
            580   585   590
Asp Thr Ala Asp Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met
        595   600   605
His Gly Asp Tyr Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu
    610   615   620
Ile Lys Ile Phe His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu
625   630   635   640
Thr Phe Ser Ser Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser
                645   650   655
Leu Ala Gln Tyr Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val
            660   665   670
Ser Lys Tyr Gln Gln Asp Gln Val Val Lys Glu Asp Asn Ile Glu Ala
        675   680   685
Val Gly Lys Lys Leu His Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser
    690   695   700
Arg Glu Tyr Asp Arg Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu
705   710   715   720
Ile Gln Met Lys Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys
                725   730   735
Ile Phe Glu Glu Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr
            740   745   750
Ile Glu Lys Phe Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile
        755   760   765
Met His Asn Tyr Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp
    770   775   780
Ser Arg Arg Arg Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu Tyr
785   790   795   800
Arg Glu Ile Asp Lys Arg Met Asn Ser Ile Lys Pro Asp Leu Ile Gln
                805   810   815
Leu Arg Lys Thr Arg Asp Gln Tyr Leu Met Trp Leu Thr Gln Lys Gly
            820   825   830
Val Arg Gln Lys Lys Leu Asn Glu Trp Leu Gly Asn Glu Asn Thr Glu
        835   840   845
Asp Gln Tyr Ser Leu Val Glu Asp Asp Glu Asp Leu Pro His His Asp
    850   855   860
Glu Lys Thr Trp Asn Val Gly Ser Ser Asn Arg Asn Lys Ala Glu Asn
865   870   875   880
Leu Leu Arg Gly Lys Arg Asp Gly Thr Phe Leu Val Arg Glu Ser Ser
                885   890   895

Lys Gln Gly Cys Tyr Ala Cys Ser Val Val Val Asp Gly Glu Val Lys
900 905 910
His Cys Val Ile Asn Lys Thr Ala Thr Gly Tyr Gly Phe Ala Glu Pro
915 920 925
Tyr Asn Leu Tyr Ser Ser Leu Lys Glu Leu Val Leu His Tyr Gln His
930 935 940
Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr
945 950 955 960
Pro Val Tyr Ala Gln Gln Arg Arg
965

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2160 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2157
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly

115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG TCG TCC ATC 768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ser Ser Ile
245 250 255

TTG CCA TTC ACG CCG CCA GTT GTG AAG AGA CTG CTG GGA TGG AAG AAG 816
Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Gly Trp Lys Lys
260 265 270

TCA GCT GGT GGG TCT GGA GGA GCA GGC GGA GGA GAG CAG AAT GGG CAG 864
Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu Gln Asn Gly Gln
275 280 285

GAA GAA AAG TGG TGT GAG AAA GCA GTG AAA AGT CTG GTG AAG AAG CTA 912
Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu Val Lys Lys Leu
290 295 300

AAG AAA ACA GGA CGA TTA GAT GAG CTT GAG AAA GCC ATC ACC ACT CAA 960
Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln
305 310 315 320

AAC TGT AAT ACT AAA TGT GTT ACC ATA CCA AGC ACT TGC TCT GAA ATT 1008
Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr Cys Ser Glu Ile
325 330 335

TGG GGA CTG AGT ACA CCA AAT ACG ATA GAT CAG TGG GAT ACA ACA GGC 1056
Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp Asp Thr Thr Gly
340 345 350

```
CTT TAC AGC TTC TCT GAA CAA ACC AGG TCT CTT GAT GGT CGT CTC CAG     1104
Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp Gly Arg Leu Gln
        355                 360                 365

GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT TGC CGA TTA TGG     1152
Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr Cys Arg Leu Trp
    370                 375                 380

CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG GCA ATT GAA AAC     1200
Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys Ala Ile Glu Asn
385                 390                 395                 400

TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA TGT GTA AAC CCT     1248
Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val Cys Val Asn Pro
                405                 410                 415

TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT CCA GTA TTA GTG     1296
Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro Pro Val Leu Val
            420                 425                 430

CCC CGA CAC ACC GAG ATC CTA ACA GAA CTT CCG CCT CTG GAT GAC TAT     1344
Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro Leu Asp Asp Tyr
        435                 440                 445

ACT CAC TCC ATT CCA GAA AAC ACT AAC TTC CCA GCA GGA ATT GAG CCA     1392
Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala Gly Ile Glu Pro
    450                 455                 460

CAG AGT AAT TAT ATT CCA GAA ACG CCA CCT CCT GGA TAT ATC AGT GAA     1440
Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly Tyr Ile Ser Glu
465                 470                 475                 480

GAT GGA GAA ACA AGT GAC CAA CAG TTG AAT CAA AGT ATG GAC ACA GGC     1488
Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser Met Asp Thr Gly
                485                 490                 495

TCT CCA GCA GAA CTA TCT CCT ACT ACT CTT TCC CCT GTT AAT CAT AGC     1536
Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro Val Asn His Ser
            500                 505                 510

TTG GAT TTA CAG CCA GTT ACT TAC TCA GAA CCT GCA TTT TGG TGT TCA     1584
Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala Phe Trp Cys Ser
        515                 520                 525

ATA GCA TAT TAT GAA TTA AAT CAG AGG GTT GGA GAA ACC TTC CAT GCA     1632
Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu Thr Phe His Ala
    530                 535                 540

TCA CAG CCC TCA CTC ACT GTA GAT GGC TTT ACA GAC CCA TCA AAT TCA     1680
Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp Pro Ser Asn Ser
545                 550                 555                 560

GAG AGG TTC TGC TTA GGT TTA CTC TCC AAT GTT AAC CGA AAT GCC ACG     1728
Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn Arg Asn Ala Thr
                565                 570                 575

GTA GAA ATG ACA AGA AGG CAT ATA GGA AGA GGA GTG CGC TTA TAC TAC     1776
Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val Arg Leu Tyr Tyr
```

```
                580                 585                 590

ATA GGT GGG GAA GTT TTT GCT GAG TGC CTA AGT GAT AGT GCA ATC TTT      1824
Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp Ser Ala Ile Phe
        595                 600                 605

GTG CAG AGC CCC AAT TGT AAT CAG AGA TAT GGC TGG CAC CCT GCA ACA      1872
Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp His Pro Ala Thr
    610                 615                 620

GTG TGT AAA ATT CCA CCA GGC TGT AAT CTG AAG ATC TTC AAC AAC CAG      1920
Val Cys Lys Ile Pro Pro Gly Cys Asn Leu Lys Ile Phe Asn Asn Gln
625                 630                 635                 640

GAA TTT GCT GCT CTT CTG GCT CAG TCT GTT AAT CAG GGT TTT GAA GCC      1968
Glu Phe Ala Ala Leu Leu Ala Gln Ser Val Asn Gln Gly Phe Glu Ala
                645                 650                 655

GTC TAT CAG CTA ACT AGA ATG TGC ACC ATA AGA ATG AGT TTT GTG AAA      2016
Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met Ser Phe Val Lys
                660                 665                 670

GGG TGG GGA GCA GAA TAC CGA AGG CAG ACG GTA ACA AGT ACT CCT TGC      2064
Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr Ser Thr Pro Cys
        675                 680                 685

TGG ATT GAA CTT CAT CTG AAT GGA CCT CTA CAG TGG TTG GAC AAA GTA      2112
Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp Leu Asp Lys Val
    690                 695                 700

TTA ACT CAG ATG GGA TCC CCT TCA GTG CGT TGC TCA AGC ATG TCA TAA      2160
Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser Ser Met Ser
705                 710                 715
```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 719 amino acids
  (B) TYPE: amino acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
```

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ser Ser Ile
245 250 255
Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Gly Trp Lys Lys
260 265 270
Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu Gln Asn Gly Gln
275 280 285
Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu Val Lys Lys Leu
290 295 300
Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln
305 310 315 320
Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr Cys Ser Glu Ile
325 330 335
Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp Asp Thr Thr Gly
340 345 350
Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp Gly Arg Leu Gln
355 360 365
Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr Cys Arg Leu Trp
370 375 380
Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys Ala Ile Glu Asn
385 390 395 400
Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val Cys Val Asn Pro
405 410 415
Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro Pro Val Leu Val
420 425 430
Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro Leu Asp Asp Tyr
435 440 445
Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala Gly Ile Glu Pro
450 455 460
Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly Tyr Ile Ser Glu
465 470 475 480
Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser Met Asp Thr Gly
485 490 495
Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro Val Asn His Ser
500 505 510
Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala Phe Trp Cys Ser
515 520 525
Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu Thr Phe His Ala
530 535 540

Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp Pro Ser Asn Ser
545 550 555 560
Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn Arg Asn Ala Thr
565 570 575
Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val Arg Leu Tyr Tyr
580 585 590
Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp Ser Ala Ile Phe
595 600 605
Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp His Pro Ala Thr
610 615 620
Val Cys Lys Ile Pro Pro Gly Cys Asn Leu Lys Ile Phe Asn Asn Gln
625 630 635 640
Glu Phe Ala Ala Leu Leu Ala Gln Ser Val Asn Gln Gly Phe Glu Ala
645 650 655
Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met Ser Phe Val Lys
660 665 670
Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr Ser Thr Pro Cys
675 680 685
Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp Leu Asp Lys Val
690 695 700
Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser Ser Met Ser
705 710 715

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2421 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2418
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys

65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG AAT TCA ACC ATG GAC 768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
245 250 255

AAT ATG TCT ATT ACG AAT ACA CCA ACA AGT AAT GAT GCC TGT CTG AGC 816
Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
260 265 270

ATT GTG CAT AGT TTG ATG TGC CAT AGA CAA GGT GGA GAG AGT GAA ACA 864
Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
275 280 285

TTT GCA AAA AGA GCA ATT GAA AGT TTG GTA AAG AAG CTG AAG GAG AAA 912
Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
290 295 300

AAA GAT GAA TTG GAT TCT TTA ATA ACA GCT ATA ACT ACA AAT GGA GCT 960
Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
305 310 315 320

CAT CCT AGT AAA TGT GTT ACC ATA CAG AGA ACA TTG GAT GGG AGG CTT 1008
His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
325 330 335

CAG GTG GCT GGT CGG AAA GGA TTT CCT CAT GTG ATC TAT GCC CGT CTC 1056
Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
340 345 350

TGG AGG TGG CCT GAT CTT CAC AAA AAT GAA CTA AAA CAT GTT AAA TAT 1104
Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val Lys Tyr
355 360 365

TGT CAG TAT GCG TTT GAC TTA AAA TGT GAT AGT GTC TGT GTG AAT CCA 1152
Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val Asn Pro
370 375 380

TAT CAC TAC GAA CGA GTT GTA TCA CCT GGA ATT GAT CTC TCA GGA TTA 1200
Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser Gly Leu
385 390 395 400

ACA CTG CAG AGT AAT GCT CCA TCA AGT ATG ATG GTG AAG GAT GAA TAT 1248
Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp Glu Tyr
405 410 415

GTG CAT GAC TTT GAG GGA CAG CCA TCG TTG TCC ACT GAA GGA CAT TCA 1296
Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly His Ser
420 425 430

ATT CAA ACC ATC CAG CAT CCA CCA AGT AAT CGT GCA TCG ACA GAG ACA 1344
Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr Glu Thr
435 440 445

TAC AGC ACC CCA GCT CTG TTA GCC CCA TCT GAG TCT AAT GCT ACC AGC 1392
Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala Thr Ser
450 455 460

ACT GCC AAC TTT CCC AAC ATT CCT GTG GCT TCC ACA AGT CAG CCT GCC 1440
Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln Pro Ala
465 470 475 480

AGT ATA CTG GGG GGC AGC CAT AGT GAA GGA CTG TTG CAG ATA GCA TCA 1488
Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile Ala Ser
485 490 495

GGG CCT CAG CCA GGA CAG CAG CAG AAT GGA TTT ACT GGT CAG CCA GCT 1536
Gly Pro Gln Pro Gly Gln Gln Gln Asn Gly Phe Thr Gly Gln Pro Ala
500 505 510

ACT TAC CAT CAT AAC AGC ACT ACC ACC TGG ACT GGA AGT AGG ACT GCA 1584
Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg Thr Ala
515 520 525

CCA TAC ACA CCT AAT TTG CCT CAC CAC CAA AAC GGC CAT CTT CAG CAC 1632
Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu Gln His

530 535 540

CAC CCG CCT ATG CCG CCC CAT CCC GGA CAT TAC TGG CCT GTT CAC AAT 1680
His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val His Asn
545 550 555 560

GAG CTT GCA TTC CAG CCT CCC ATT TCC AAT CAT CCT GCT CCT GAG TAT 1728
Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro Glu Tyr
565 570 575

TGG TGT TCC ATT GCT TAC TTT GAA ATG GAT GTT CAG GTA GGA GAG ACA 1776
Trp Cys Ser Ile Ala Tyr Phe Glu Met Asp Val Gln Val Gly Glu Thr
580 585 590

TTT AAG GTT CCT TCA AGC TGC CCT ATT GTT ACT GTT GAT GGA TAC GTG 1824
Phe Lys Val Pro Ser Ser Cys Pro Ile Val Thr Val Asp Gly Tyr Val
595 600 605

GAC CCT TCT GGA GGA GAT CGC TTT TGT TTG GGT CAA CTC TCC AAT GTC 1872
Asp Pro Ser Gly Gly Asp Arg Phe Cys Leu Gly Gln Leu Ser Asn Val
610 615 620

CAC AGG ACA GAA GCC ATT GAG AGA GCA AGG TTG CAC ATA GGC AAA GGT 1920
His Arg Thr Glu Ala Ile Glu Arg Ala Arg Leu His Ile Gly Lys Gly
625 630 635 640

GTG CAG TTG GAA TGT AAA GGT GAA GGT GAT GTT TGG GTC AGG TGC CTT 1968
Val Gln Leu Glu Cys Lys Gly Glu Gly Asp Val Trp Val Arg Cys Leu
645 650 655

AGT GAC CAC GCG GTC TTT GTA CAG AGT TAC TAC TTA GAC AGA GAA GCT 2016
Ser Asp His Ala Val Phe Val Gln Ser Tyr Tyr Leu Asp Arg Glu Ala
660 665 670

GGG CGT GCA CCT GGA GAT GCT GTT CAT AAG ATC TAC CCA AGT GCA TAT 2064
Gly Arg Ala Pro Gly Asp Ala Val His Lys Ile Tyr Pro Ser Ala Tyr
675 680 685

ATA AAG GTC TTT GAT TTG CGT CAG TGT CAT CGA CAG ATG CAG CAG CAG 2112
Ile Lys Val Phe Asp Leu Arg Gln Cys His Arg Gln Met Gln Gln Gln
690 695 700

GCG GCT ACT GCA CAA GCT GCA GCA GCT GCC CAG GCA GCA GCC GTG GCA 2160
Ala Ala Thr Ala Gln Ala Ala Ala Ala Ala Gln Ala Ala Ala Val Ala
705 710 715 720

GGA AAC ATC CCT GGC CCA GGA TCA GTA GGT GGA ATA GCT CCA GCT ATC 2208
Gly Asn Ile Pro Gly Pro Gly Ser Val Gly Gly Ile Ala Pro Ala Ile
725 730 735

AGT CTG TCA GCT GCT GCT GGA ATT GGT GTT GAT GAC CTT CGT CGC TTA 2256
Ser Leu Ser Ala Ala Ala Gly Ile Gly Val Asp Asp Leu Arg Arg Leu
740 745 750

TGC ATA CTC AGG ATG AGT TTT GTG AAA GGC TGG GGA CCG GAT TAC CCA 2304
Cys Ile Leu Arg Met Ser Phe Val Lys Gly Trp Gly Pro Asp Tyr Pro
755 760 765

AGA CAG AGC ATC AAA GAA ACA CCT TGC TGG ATT GAA ATT CAC TTA CAC 2352
Arg Gln Ser Ile Lys Glu Thr Pro Cys Trp Ile Glu Ile His Leu His
770 775 780

CGG GCC CTC CAG CTC CTA GAC GAA GTA CTT CAT ACC ATG CCG ATT GCA 2400
Arg Ala Leu Gln Leu Leu Asp Glu Val Leu His Thr Met Pro Ile Ala
785 790 795 800

GAC CCA CAA CCT TTA GAC TGA 2421
Asp Pro Gln Pro Leu Asp
805

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 806 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
245 250 255

Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
260 265 270
Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
275 280 285
Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
290 295 300
Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
305 310 315 320
His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
325 330 335
Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
340 345 350
Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val Lys Tyr
355 360 365
Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val Asn Pro
370 375 380
Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser Gly Leu
385 390 395 400
Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp Glu Tyr
405 410 415
Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly His Ser
420 425 430
Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr Glu Thr
435 440 445
Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala Thr Ser
450 455 460
Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln Pro Ala
465 470 475 480
Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile Ala Ser
485 490 495
Gly Pro Gln Pro Gly Gln Gln Gln Asn Gly Phe Thr Gly Gln Pro Ala
500 505 510
Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg Thr Ala
515 520 525
Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu Gln His
530 535 540
His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val His Asn
545 550 555 560
Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro Glu Tyr
565 570 575
Trp Cys Ser Ile Ala Tyr Phe Glu Met Asp Val Gln Val Gly Glu Thr
580 585 590
Phe Lys Val Pro Ser Ser Cys Pro Ile Val Thr Val Asp Gly Tyr Val
595 600 605
Asp Pro Ser Gly Gly Asp Arg Phe Cys Leu Gly Gln Leu Ser Asn Val
610 615 620
His Arg Thr Glu Ala Ile Glu Arg Ala Arg Leu His Ile Gly Lys Gly
625 630 635 640
Val Gln Leu Glu Cys Lys Gly Glu Gly Asp Val Trp Val Arg Cys Leu
645 650 655
Ser Asp His Ala Val Phe Val Gln Ser Tyr Tyr Leu Asp Arg Glu Ala
660 665 670
Gly Arg Ala Pro Gly Asp Ala Val His Lys Ile Tyr Pro Ser Ala Tyr
675 680 685
Ile Lys Val Phe Asp Leu Arg Gln Cys His Arg Gln Met Gln Gln Gln
690 695 700
Ala Ala Thr Ala Gln Ala Ala Ala Ala Ala Gln Ala Ala Ala Val Ala
705 710 715 720

Gly Asn Ile Pro Gly Pro Gly Ser Val Gly Gly Ile Ala Pro Ala Ile
725 730 735
Ser Leu Ser Ala Ala Ala Gly Ile Gly Val Asp Asp Leu Arg Arg Leu
740 745 750
Cys Ile Leu Arg Met Ser Phe Val Lys Gly Trp Gly Pro Asp Tyr Pro
755 760 765
Arg Gln Ser Ile Lys Glu Thr Pro Cys Trp Ile Glu Ile His Leu His
770 775 780
Arg Ala Leu Gln Leu Leu Asp Glu Val Leu His Thr Met Pro Ile Ala
785 790 795 800
Asp Pro Gln Pro Leu Asp
805

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3117
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT ACC ATG GCG GGC TGG ATC CAG GCC CAG CAG CTG CAG 768
Gly Leu Arg Ser Thr Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln
245 250 255

GGA GAC GCG CTG CGC CAG ATG CAG GTG CTG TAC GGC CAG CAC TTC CCC 816
Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro
260 265 270

ATC GAG GTC CGG CAC TAC TTG GCC CAG TGG ATT GAG AGC CAG CCA TGG 864
Ile Glu Val Arg His Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp
275 280 285

GAT GCC ATT GAC TTG GAC AAT CCC CAG GAC AGA GCC CAA GCC ACC CAG 912
Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln
290 295 300

CTC CTG GAG GGC CTG GTG CAG GAG CTG CAG AAG AAG GCG GAG CAC CAG 960
Leu Leu Glu Gly Leu Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln
305 310 315 320

GTG GGG GAA GAT GGG TTT TTA CTG AAG ATC AAG CTG GGG CAC TAC GCC 1008
Val Gly Glu Asp Gly Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala
325 330 335

ACG CAG CTC CAG AAA ACA TAT GAC CGC TGC CCC CTG GAG CTG GTC CGC 1056
Thr Gln Leu Gln Lys Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg

340 345 350

TGC ATC CGG CAC ATT CTG TAC AAT GAA CAG AGG CTG GTC CGA GAA GCC 1104
Cys Ile Arg His Ile Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala
355 360 365

AAC AAT TGC AGC TCT CCG GCT GGG ATC CTG GTT GAC GCC ATG TCC CAG 1152
Asn Asn Cys Ser Ser Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln
370 375 380

AAG CAC CTT CAG ATC AAC CAG ACA TTT GAG GAG CTG CGA CTG GTC ACG 1200
Lys His Leu Gln Ile Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr
385 390 395 400

CAG GAC ACA GAG AAT GAG CTG AAG AAA CTG CAG CAG ACT CAG GAG TAC 1248
Gln Asp Thr Glu Asn Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr
405 410 415

TTC ATC ATC CAG TAC CAG GAG AGC CTG AGG ATC CAA GCT CAG TTT GCC 1296
Phe Ile Ile Gln Tyr Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala
420 425 430

CAG CTG GCC CAG CTG AGC CCC CAG GAG CGT CTG AGC CGG GAG ACG GCC 1344
Gln Leu Ala Gln Leu Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala
435 440 445

CTC CAG CAG AAG CAG GTG TCT CTG GAG GCC TGG TTG CAG CGT GAG GCA 1392
Leu Gln Gln Lys Gln Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala
450 455 460

CAG ACA CTG CAG CAG TAC CGC GTG GAG CTG GCC GAG AAG CAC CAG AAG 1440
Gln Thr Leu Gln Gln Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys
465 470 475 480

ACC CTG CAG CTG CTG CGG AAG CAG CAG ACC ATC ATC CTG GAT GAC GAG 1488
Thr Leu Gln Leu Leu Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu
485 490 495

CTG ATC CAG TGG AAG CGG CGG CAG CAG CTG GCC GGG AAC GGC GGG CCC 1536
Leu Ile Gln Trp Lys Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro
500 505 510

CCC GAG GGC AGC CTG GAC GTG CTA CAG TCC TGG TGT GAG AAG TTG GCC 1584
Pro Glu Gly Ser Leu Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala
515 520 525

GAG ATC ATC TGG CAG AAC CGG CAG CAG ATC CGC AGG GCT GAG CAC CTC 1632
Glu Ile Ile Trp Gln Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu
530 535 540

TGC CAG CAG CTG CCC ATC CCC GGC CCA GTG GAG GAG ATG CTG GCC GAG 1680
Cys Gln Gln Leu Pro Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu
545 550 555 560

GTC AAC GCC ACC ATC ACG GAC ATT ATC TCA GCC CTG GTG ACC AGC ACA 1728
Val Asn Ala Thr Ile Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr
565 570 575

```
TTC ATC ATT GAG AAG CAG CCT CCT CAG GTC CTG AAG ACC CAG ACC AAG     1776
Phe Ile Ile Glu Lys Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys
            580                 585                 590

TTT GCA GCC ACC GTA CGC CTG CTG GTG GGC GGG AAG CTG AAC GTG CAC     1824
Phe Ala Ala Thr Val Arg Leu Leu Val Gly Gly Lys Leu Asn Val His
        595                 600                 605

ATG AAT CCC CCC CAG GTG AAG GCC ACC ATC ATC AGT GAG CAG CAG GCC     1872
Met Asn Pro Pro Gln Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala
    610                 615                 620

AAG TCT CTG CTT AAA AAT GAG AAC ACC CGC AAC GAG TGC AGT GGT GAG     1920
Lys Ser Leu Leu Lys Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu
625                 630                 635                 640

ATC CTG AAC AAC TGC TGC GTG ATG GAG TAC CAC CAA GCC ACG GGC ACC     1968
Ile Leu Asn Asn Cys Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr
                645                 650                 655

CTC AGT GCC CAC TTC AGG AAC ATG TCA CTG AAG AGG ATC AAG CGT GCT     2016
Leu Ser Ala His Phe Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala
            660                 665                 670

GAC CGG CGG GGT GCA GAG TCC GTG ACA GAG GAG AAG TTC ACA GTC CTG     2064
Asp Arg Arg Gly Ala Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu
        675                 680                 685

TTT GAG TCT CAG TTC AGT GTT GGC AGC AAT GAG CTT GTG TTC CAG GTG     2112
Phe Glu Ser Gln Phe Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val
    690                 695                 700

AAG ACT CTG TCC CTA CCT GTG GTT GTC ATC GTC CAC GGC AGC CAG GAC     2160
Lys Thr Leu Ser Leu Pro Val Val Val Ile Val His Gly Ser Gln Asp
705                 710                 715                 720

CAC AAT GCC ACG GCT ACT GTG CTG TGG GAC AAT GCC TTT GCT GAG CCG     2208
His Asn Ala Thr Ala Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro
                725                 730                 735

GGC AGG GTG CCA TTT GCC GTG CCT GAC AAA GTG CTG TGG CCG CAG CTG     2256
Gly Arg Val Pro Phe Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu
            740                 745                 750

TGT GAG GCG CTC AAC ATG AAA TTC AAG GCC GAA GTG CAG AGC AAC CGG     2304
Cys Glu Ala Leu Asn Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg
        755                 760                 765

GGC CTG ACC AAG GAG AAC CTC GTG TTC CTG GCG CAG AAA CTG TTC AAC     2352
Gly Leu Thr Lys Glu Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn
    770                 775                 780

AAC AGC AGC AGC CAC CTG GAG GAC TAC AGT GGC CTG TCC GTG TCC TGG     2400
Asn Ser Ser Ser His Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp
785                 790                 795                 800

TCC CAG TTC AAC AGG GAG AAC TTG CCG GGC TGG AAC TAC ACC TTC TGG     2448
Ser Gln Phe Asn Arg Glu Asn Leu Pro Gly Trp Asn Tyr Thr Phe Trp
```

805 810 815

CAG TGG TTT GAC GGG GTG ATG GAG GTG TTG AAG AAG CAC CAC AAG CCC 2496
Gln Trp Phe Asp Gly Val Met Glu Val Leu Lys Lys His His Lys Pro
820 825 830

CAC TGG AAT GAT GGG GCC ATC CTA GGT TTT GTG AAT AAG CAA CAG GCC 2544
His Trp Asn Asp Gly Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala
835 840 845

CAC GAC CTG CTC ATC AAC AAG CCC GAC GGG ACC TTC TTG TTG CGC TTT 2592
His Asp Leu Leu Ile Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe
850 855 860

AGT GAC TCA GAA ATC GGG GGC ATC ACC ATC GCC TGG AAG TTT GAC TCC 2640
Ser Asp Ser Glu Ile Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser
865 870 875 880

CCG GAA CGC AAC CTG TGG AAC CTG AAA CCA TTC ACC ACG CGG GAT TTC 2688
Pro Glu Arg Asn Leu Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe
885 890 895

TCC ATC AGG TCC CTG GCT GAC CGG CTG GGG GAC CTG AGC TAT CTC ATC 2736
Ser Ile Arg Ser Leu Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile
900 905 910

TAT GTG TTT CCT GAC CGC CCC AAG GAT GAG GTC TTC TCC AAG TAC TAC 2784
Tyr Val Phe Pro Asp Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr
915 920 925

ACT CCT GTG CTG GCT AAA GCT GTT GAT GGA TAT GTG AAA CCA CAG ATC 2832
Thr Pro Val Leu Ala Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile
930 935 940

AAG CAA GTG GTC CCT GAG TTT GTG AAT GCA TCT GCA GAT GCT GGG GGC 2880
Lys Gln Val Val Pro Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly
945 950 955 960

AGC AGC GCC ACG TAC ATG GAC CAG GCC CCC TCC CCA GCT GTG TGC CCC 2928
Ser Ser Ala Thr Tyr Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro
965 970 975

CAG GCT CCC TAT AAC ATG TAC CCA CAG AAC CCT GAC CAT GTA CTC GAT 2976
Gln Ala Pro Tyr Asn Met Tyr Pro Gln Asn Pro Asp His Val Leu Asp
980 985 990

CAG GAT GGA GAA TTC GAC CTG GAT GAG ACC ATG GAT GTG GCC AGG CAC 3024
Gln Asp Gly Glu Phe Asp Leu Asp Glu Thr Met Asp Val Ala Arg His
995 1000 1005

GTG GAG GAA CTC TTA CGC CGA CCA ATG GAC AGT CTT GAC TCC CGC CTC 3072
Val Glu Glu Leu Leu Arg Arg Pro Met Asp Ser Leu Asp Ser Arg Leu
1010 1015 1020

TCG CCC CCT GCC GGT CTT TTC ACC TCT GCC AGA GGC TCC CTC TCA TGA 3120
Ser Pro Pro Ala Gly Leu Phe Thr Ser Ala Arg Gly Ser Leu Ser
1025 1030 1035 1

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1039 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Thr Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln
                245                 250                 255
Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro
            260                 265                 270
Ile Glu Val Arg His Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp
        275                 280                 285
Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln
    290                 295                 300
Leu Leu Glu Gly Leu Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln
305                 310                 315                 320
Val Gly Glu Asp Gly Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala
                325                 330                 335
Thr Gln Leu Gln Lys Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg
            340                 345                 350
```

Cys Ile Arg His Ile Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala
355 360 365
Asn Asn Cys Ser Ser Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln
370 375 380
Lys His Leu Gln Ile Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr
385 390 395 400
Gln Asp Thr Glu Asn Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr
405 410 415
Phe Ile Ile Gln Tyr Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala
420 425 430
Gln Leu Ala Gln Leu Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala
435 440 445
Leu Gln Gln Lys Gln Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala
450 455 460
Gln Thr Leu Gln Gln Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys
465 470 475 480
Thr Leu Gln Leu Leu Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu
485 490 495
Leu Ile Gln Trp Lys Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro
500 505 510
Pro Glu Gly Ser Leu Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala
515 520 525
Glu Ile Ile Trp Gln Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu
530 535 540
Cys Gln Gln Leu Pro Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu
545 550 555 560
Val Asn Ala Thr Ile Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr
565 570 575
Phe Ile Ile Glu Lys Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys
580 585 590
Phe Ala Ala Thr Val Arg Leu Leu Val Gly Gly Lys Leu Asn Val His
595 600 605
Met Asn Pro Pro Gln Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala
610 615 620
Lys Ser Leu Leu Lys Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu
625 630 635 640
Ile Leu Asn Asn Cys Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr
645 650 655
Leu Ser Ala His Phe Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala
660 665 670
Asp Arg Arg Gly Ala Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu
675 680 685
Phe Glu Ser Gln Phe Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val
690 695 700
Lys Thr Leu Ser Leu Pro Val Val Val Ile Val His Gly Ser Gln Asp
705 710 715 720
His Asn Ala Thr Ala Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro
725 730 735
Gly Arg Val Pro Phe Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu
740 745 750
Cys Glu Ala Leu Asn Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg
755 760 765
Gly Leu Thr Lys Glu Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn
770 775 780
Asn Ser Ser Ser His Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp
785 790 795 800
Ser Gln Phe Asn Arg Glu Asn Leu Pro Gly Trp Asn Tyr Thr Phe Trp
805 810 815

Gln Trp Phe Asp Gly Val Met Glu Val Leu Lys Lys His His Lys Pro
820 825 830
His Trp Asn Asp Gly Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala
835 840 845
His Asp Leu Leu Ile Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe
850 855 860
Ser Asp Ser Glu Ile Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser
865 870 875 880
Pro Glu Arg Asn Leu Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe
885 890 895
Ser Ile Arg Ser Leu Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile
900 905 910
Tyr Val Phe Pro Asp Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr
915 920 925
Thr Pro Val Leu Ala Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile
930 935 940
Lys Gln Val Val Pro Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly
945 950 955 960
Ser Ser Ala Thr Tyr Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro
965 970 975
Gln Ala Pro Tyr Asn Met Tyr Pro Gln Asn Pro Asp His Val Leu Asp
980 985 990
Gln Asp Gly Glu Phe Asp Leu Asp Glu Thr Met Asp Val Ala Arg His
995 1000 1005
Val Glu Glu Leu Leu Arg Arg Pro Met Asp Ser Leu Asp Ser Arg Leu
1010 1015 1020
Ser Pro Pro Ala Gly Leu Phe Thr Ser Ala Arg Gly Ser Leu Ser
025 1030 1035 1

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1875 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1872
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

ATG GCG GCG GCG GCG GCG GCT CCG GGG GGC GGG GGC GGG GAG CCC AGG 48
Met Ala Ala Ala Ala Ala Ala Pro Gly Gly Gly Gly Gly Glu Pro Arg
1 5 10 15

GGA ACT GCT GGG GTC GTC CCG GTG GTC CCC GGG GAG GTG GAG GTG GTG 96
Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val
20 25 30

AAG GGG CAG CCA TTC GAT GTG GGC CCA CGC TAC ACG CAG CTG CAG TAC 144
Lys Gly Gln Pro Phe Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr
35 40 45

ATC GGC GAG GGC GCG TAC GGC ATG GTC AGC TCA GCT TAT GAC CAC GTG 192
Ile Gly Glu Gly Ala Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val
50 55 60

CGC AAG ACC AGA GTG GCC ATC AAG AAG ATC AGC CCC TTT GAG CAT CAA 240
Arg Lys Thr Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln
65 70 75 80

ACC TAC TGT CAG CGC ACG CTG AGG GAG ATC CAG ATC TTG CTG CGA TTC 288
Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe
85 90 95

CGC CAT GAG AAT GTT ATA GGC ATC CGA GAC ATC CTC AGA GCG CCC ACC 336
Arg His Glu Asn Val Ile Gly Ile Arg Asp Ile Leu Arg Ala Pro Thr
100 105 110

CTG GAA GCC ATG AGA GAT GTT TAC ATT GTT CAG GAC CTC ATG GAG ACA 384
Leu Glu Ala Met Arg Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr
115 120 125

GAC CTG TAC AAG CTG CTT AAA AGC CAG CAG CTG AGC AAT GAC CAC ATC 432
Asp Leu Tyr Lys Leu Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile
130 135 140

TGC TAC TTC CTC TAC CAG ATC CTC CGG GGC CTC AAG TAT ATA CAC TCA 480
Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser
145 150 155 160

GCC AAT GTG CTG CAC CGG GAC CTG AAG CCT TCC AAT CTG CTT ATC AAC 528
Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn
165 170 175

ACC ACC TGC GAC CTT AAG ATC TGT GAT TTT GGC CTG GCC CGG ATT GCT 576
Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala
180 185 190

GAC CCT GAG CAC GAC CAC ACT GGC TTT CTG ACG GAG TAT GTG GCC ACA 624
Asp Pro Glu His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr
195 200 205

CGC TGG TAC CGA GCC CCA GAG ATC ATG CTT AAT TCC AAG GGC TAC ACC 672
Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr
210 215 220

AAA TCC ATC GAC ATC TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC 720
Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu
225 230 235 240

TCC AAC CGG CCC ATC TTC CCC GGC AAG CAC TAC CTG GAC CAG CTC AAC 768
Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn
245 250 255

CAC ATT CTA GGT ATC TTG GGT TCC CCA TCC CAG GAG GAC CTT AAT TGC 816
His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys
260 265 270

ATC ATT AAC ATG AAG GCC CGA AAC TAC CTG CAG TCT CTG CCC TCG AAA 864
Ile Ile Asn Met Lys Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys

275 280 285

ACC AAG GTG GCT TGG GCC AAG CTC TTT CCT AAA TCT GAC TCC AAA GCT 912
Thr Lys Val Ala Trp Ala Lys Leu Phe Pro Lys Ser Asp Ser Lys Ala
290 295 300

CTT GAC CTG CTG GAC CGG ATG TTA ACC TTC AAC CCA AAC AAG CGC ATC 960
Leu Asp Leu Leu Asp Arg Met Leu Thr Phe Asn Pro Asn Lys Arg Ile
305 310 315 320

ACA GTA GAG GAA GCG CTG GCT CAC CCT TAC CTG GAA CAG TAC TAC GAT 1008
Thr Val Glu Glu Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp
325 330 335

CCG ACA GAT GAG CCA GTG GCC GAG GAG CCA TTC ACC TTC GAC ATG GAG 1056
Pro Thr Asp Glu Pro Val Ala Glu Glu Pro Phe Thr Phe Asp Met Glu
340 345 350

CTG GAT GAC CTC CCC AAG GAG CGG CTG AAG GAG TTG ATC TTC CAG GAG 1104
Leu Asp Asp Leu Pro Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu
355 360 365

ACA GCC CGC TTC CAG CCA GGG GCG CCA GAG GGC CCC GGG CGC GCC ATG 1152
Thr Ala Arg Phe Gln Pro Gly Ala Pro Glu Gly Pro Gly Arg Ala Met
370 375 380

AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT CTT GTT GAA 1200
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
385 390 395 400

TTA GAT GGC GAT GTT AAT GGG CAA AAA TTC TCT GTT AGT GGA GAG GGT 1248
Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val Ser Gly Glu Gly
405 410 415

GAA GGT GAT GCA ACA TAC GGA AAA CTT ACC CTT AAA TTT ATT TGC ACT 1296
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
420 425 430

ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT GTC ACT ACT CTC ACT 1344
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
435 440 445

TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG AAA CAG CAT 1392
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
450 455 460

GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG GAA AGA ACT 1440
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
465 470 475 480

ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG 1488
Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
485 490 495

TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA GGT ATT GAT 1536
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
500 505 510

```
TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA TAC AAT TAT     1584
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu Tyr Asn Tyr
        515                 520                 525

AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC ATC     1632
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys Asn Gly Ile
    530                 535                 540

AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA     1680
Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly Ser Val Gln
545                 550                 555                 560

TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC     1728
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
                565                 570                 575

CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC CTT TCC AAA     1776
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
            580                 585                 590

GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG TTT GTA ACA     1824
Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu Phe Val Thr
        595                 600                 605

GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA CCT CAG GAG T   1873
Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys Pro Gln Glu
    610                 615                 620

AA                                                                   1875
```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 624 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```
Met Ala Ala Ala Ala Ala Ala Pro Gly Gly Gly Gly Gly Glu Pro Arg
 1               5                  10                  15
Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val
            20                  25                  30
Lys Gly Gln Pro Phe Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr
        35                  40                  45
Ile Gly Glu Gly Ala Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val
    50                  55                  60
Arg Lys Thr Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln
65                  70                  75                  80
Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe
                85                  90                  95
Arg His Glu Asn Val Ile Gly Ile Arg Asp Ile Leu Arg Ala Pro Thr
            100                 105                 110
Leu Glu Ala Met Arg Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr
```

```
        115                 120                 125
Asp Leu Tyr Lys Leu Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile
    130                 135                 140
Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser
145                 150                 155                 160
Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn
                165                 170                 175
Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala
            180                 185                 190
Asp Pro Glu His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr
        195                 200                 205
Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr
    210                 215                 220
Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu
225                 230                 235                 240
Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn
                245                 250                 255
His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys
            260                 265                 270
Ile Ile Asn Met Lys Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys
        275                 280                 285
Thr Lys Val Ala Trp Ala Lys Leu Phe Pro Lys Ser Asp Ser Lys Ala
    290                 295                 300
Leu Asp Leu Leu Asp Arg Met Leu Thr Phe Asn Pro Asn Lys Arg Ile
305                 310                 315                 320
Thr Val Glu Glu Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp
                325                 330                 335
Pro Thr Asp Glu Pro Val Ala Glu Glu Pro Phe Thr Phe Asp Met Glu
            340                 345                 350
Leu Asp Asp Leu Pro Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu
        355                 360                 365
Thr Ala Arg Phe Gln Pro Gly Ala Pro Glu Gly Pro Gly Arg Ala Met
    370                 375                 380
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
385                 390                 395                 400
Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val Ser Gly Glu Gly
                405                 410                 415
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
            420                 425                 430
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
        435                 440                 445
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
    450                 455                 460
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
465                 470                 475                 480
Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
                485                 490                 495
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
            500                 505                 510
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu Tyr Asn Tyr
        515                 520                 525
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys Asn Gly Ile
    530                 535                 540
Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly Ser Val Gln
545                 550                 555                 560
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
                565                 570                 575
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
```

```
        580                          585                     590
Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu Phe Val Thr
    595                     600                     605
Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys Pro Gln Glu
610                     615                     620
```

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1815 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1811
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```
ATG GCG GCG GCG GCG GCG GCG GGC CCG GAG ATG GTC CGC GGG CAG GTG      48
Met Ala Ala Ala Ala Ala Ala Gly Pro Glu Met Val Arg Gly Gln Val
 1               5                  10                  15

TTC GAC GTG GGG CCG CGC TAC ACT AAT CTC TCG TAC ATC GGA GAA GGC      96
Phe Asp Val Gly Pro Arg Tyr Thr Asn Leu Ser Tyr Ile Gly Glu Gly
            20                  25                  30

GCC TAC GGC ATG GTT TGT TCT GCT TAT GAT AAT CTC AAC AAA GTT CGA     144
Ala Tyr Gly Met Val Cys Ser Ala Tyr Asp Asn Leu Asn Lys Val Arg
        35                  40                  45

GTT GCT ATC AAG AAA ATC AGT CCT TTT GAG CAC CAG ACC TAC TGT CAG     192
Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr Tyr Cys Gln
    50                  55                  60

AGA ACC CTG AGA GAG ATA AAA ATC CTA CTG CGC TTC AGA CAT GAG AAC     240
Arg Thr Leu Arg Glu Ile Lys Ile Leu Leu Arg Phe Arg His Glu Asn
65                  70                  75                  80

ATC ATC GGC ATC AAT GAC ATC ATC CGG GCA CCA ACC ATT GAG CAG ATG     288
Ile Ile Gly Ile Asn Asp Ile Ile Arg Ala Pro Thr Ile Glu Gln Met
                85                  90                  95

AAA GAT GTA TAT ATA GTA CAG GAC CTC ATG GAG ACA GAT CTT TAC AAG     336
Lys Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp Leu Tyr Lys
            100                 105                 110

CTC TTG AAG ACA CAG CAC CTC AGC AAT GAT CAT ATC TGC TAT TTT CTT     384
Leu Leu Lys Thr Gln His Leu Ser Asn Asp His Ile Cys Tyr Phe Leu
        115                 120                 125

TAT CAG ATC CTG AGA GGA TTA AAG TAT ATA CAT TCA GCT AAT GTT CTG     432
Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu
    130                 135                 140
```

```
CAC CGT GAC CTC AAG CCT TCC AAC CTC CTG CTG AAC ACC ACT TGT GAT      480
His Arg Asp Leu Lys Pro Ser Asn Leu Leu Leu Asn Thr Thr Cys Asp
145                 150                 155                 160

CTC AAG ATC TGT GAC TTT GGC CTT GCC CGT GTT GCA GAT CCA GAC CAT      528
Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Val Ala Asp Pro Asp His
                165                 170                 175

GAT CAT ACA GGG TTC TTG ACA GAG TAT GTA GCC ACG CGT TGG TAC AGA      576
Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg
            180                 185                 190

GCT CCA GAA ATT ATG TTG AAT TCC AAG GGT TAT ACC AAG TCC ATT GAT      624
Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp
        195                 200                 205

ATT TGG TCT GTG GGC TGC ATC CTG GCA GAG ATG CTA TCC AAC AGG CCT      672
Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn Arg Pro
    210                 215                 220

ATC TTC CCA GGA AAG CAT TAC CTT GAC CAG CTG AAT CAC ATC CTG GGT      720
Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly
225                 230                 235                 240

ATT CTT GGA TCT CCA TCA CAG GAA GAT CTG AAT TGT ATA ATA AAT TTA      768
Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Leu
                245                 250                 255

AAA GCT AGA AAC TAT TTG CTT TCT CTC CCG CAC AAA AAT AAG GTG CCG      816
Lys Ala Arg Asn Tyr Leu Leu Ser Leu Pro His Lys Asn Lys Val Pro
            260                 265                 270

TGG AAC AGG TTG TTC CCA AAC GCT GAC TCC AAA GCT CTG GAT TTA CTG      864
Trp Asn Arg Leu Phe Pro Asn Ala Asp Ser Lys Ala Leu Asp Leu Leu
        275                 280                 285

GAT AAA ATG TTG ACA TTT AAC CCT CAC AAG AGG ATT GAA GTT GAA CAG      912
Asp Lys Met Leu Thr Phe Asn Pro His Lys Arg Ile Glu Val Glu Gln
    290                 295                 300

GCT CTG GCC CAC CCG TAC CTG GAG CAG TAT TAT GAC CCA AGT GAT GAG      960
Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro Ser Asp Glu
305                 310                 315                 320

CCC ATT GCT GAA GCA CCA TTC AAG TTT GAC ATG GAG CTG GAC GAC TTA     1008
Pro Ile Ala Glu Ala Pro Phe Lys Phe Asp Met Glu Leu Asp Asp Leu
                325                 330                 335

CCT AAG GAG AAG CTC AAA GAA CTC ATT TTT GAA GAG ACT GCT CGA TTC     1056
Pro Lys Glu Lys Leu Lys Glu Leu Ile Phe Glu Glu Thr Ala Arg Phe
            340                 345                 350

CAG CCA GGA TAC AGA TCT ATG GAT CCA CCG GTC GCC ACC ATG GTG AGC     1104
Gln Pro Gly Tyr Arg Ser Met Asp Pro Pro Val Ala Thr Met Val Ser
        355                 360                 365

AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG     1152
```

Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu
370 375 380

GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG 1200
Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu
385 390 395 400

GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC 1248
Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr
405 410 415

GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC 1296
Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr
420 425 430

GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC 1344
Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp
435 440 445

TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC 1392
Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile
450 455 460

TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC 1440
Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe
465 470 475 480

GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC 1488
Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe
485 490 495

AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC 1536
Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn
500 505 510

AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG 1584
Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys
515 520 525

GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC 1632
Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu
530 535 540

GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG 1680
Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu
545 550 555 560

CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC 1728
Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp
565 570 575

CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC 1776
Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala
580 585 590

GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AA GTAA 1815
Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
595 600

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 604 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

```
Met Ala Ala Ala Ala Ala Ala Gly Pro Glu Met Val Arg Gly Gln Val
 1               5                  10                  15
Phe Asp Val Gly Pro Arg Tyr Thr Asn Leu Ser Tyr Ile Gly Glu Gly
            20                  25                  30
Ala Tyr Gly Met Val Cys Ser Ala Tyr Asp Asn Leu Asn Lys Val Arg
        35                  40                  45
Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr Tyr Cys Gln
    50                  55                  60
Arg Thr Leu Arg Glu Ile Lys Ile Leu Leu Arg Phe Arg His Glu Asn
65                  70                  75                  80
Ile Ile Gly Ile Asn Asp Ile Ile Arg Ala Pro Thr Ile Glu Gln Met
                85                  90                  95
Lys Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp Leu Tyr Lys
            100                 105                 110
Leu Leu Lys Thr Gln His Leu Ser Asn Asp His Ile Cys Tyr Phe Leu
        115                 120                 125
Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu
    130                 135                 140
His Arg Asp Leu Lys Pro Ser Asn Leu Leu Leu Asn Thr Thr Cys Asp
145                 150                 155                 160
Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Val Ala Asp Pro Asp His
                165                 170                 175
Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg
            180                 185                 190
Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp
        195                 200                 205
Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn Arg Pro
    210                 215                 220
Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly
225                 230                 235                 240
Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Leu
                245                 250                 255
Lys Ala Arg Asn Tyr Leu Leu Ser Leu Pro His Lys Asn Lys Val Pro
            260                 265                 270
Trp Asn Arg Leu Phe Pro Asn Ala Asp Ser Lys Ala Leu Asp Leu Leu
        275                 280                 285
Asp Lys Met Leu Thr Phe Asn Pro His Lys Arg Ile Glu Val Glu Gln
    290                 295                 300
Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro Ser Asp Glu
305                 310                 315                 320
Pro Ile Ala Glu Ala Pro Phe Lys Phe Asp Met Glu Leu Asp Asp Leu
                325                 330                 335
Pro Lys Glu Lys Leu Lys Glu Leu Ile Phe Glu Glu Thr Ala Arg Phe
```

```
            340                 345                 350
Gln Pro Gly Tyr Arg Ser Met Asp Pro Pro Val Ala Thr Met Val Ser
        355                 360                 365
Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu
    370                 375                 380
Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu
385                 390                 395                 400
Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr
                405                 410                 415
Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr
            420                 425                 430
Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp
        435                 440                 445
Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile
    450                 455                 460
Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe
465                 470                 475                 480
Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe
                485                 490                 495
Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn
            500                 505                 510
Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys
        515                 520                 525
Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu
    530                 535                 540
Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu
545                 550                 555                 560
Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp
                565                 570                 575
Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala
            580                 585                 590
Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
        595                 600
```

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 2511 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

  (A) NAME/KEY: Coding Sequence
  (B) LOCATION: 1...2508
  (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

```
ATG GAG CTG GAA AAC ATC GTG GCC AAC ACG GTC TTG CTG AAA GCC AGG      48
Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg
 1               5                  10                  15

GAA GGG GGC GGA GGA AAG CGC AAA GGG AAA AGC AAG AAG TGG AAA GAA      96
Glu Gly Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu
            20                  25                  30
```

ATC CTG AAG TTC CCT CAC ATT AGC CAG TGT GAA GAC CTC CGA AGG ACC 144
Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr
35 40 45

ATA GAC AGA GAT TAC TGC AGT TTA TGT GAC AAG CAG CCA ATC GGG AGG 192
Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg
50 55 60

CTG CTT TTC CGG CAG TTT TGT GAA ACC AGG CCT GGG CTG GAG TGT TAC 240
Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr
65 70 75 80

ATT CAG TTC CTG GAC TCC GTG GCA GAA TAT GAA GTT ACT CCA GAT GAA 288
Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu
85 90 95

AAA CTG GGA GAG AAA GGG AAG GAA ATT ATG ACC AAG TAC CTC ACC CCA 336
Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro
100 105 110

AAG TCC CCT GTT TTC ATA GCC CAA GTT GGC CAA GAC CTG GTC TCC CAG 384
Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln
115 120 125

ACG GAG GAG AAG CTC CTA CAG AAG CCG TGC AAA GAA CTC TTT TCT GCC 432
Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala
130 135 140

TGT GCA CAG TCT GTC CAC GAG TAC CTG AGG GGA GAA CCA TTC CAC GAA 480
Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu
145 150 155 160

TAT CTG GAC AGC ATG TTT TTT GAC CGC TTT CTC CAG TGG AAG TGG TTG 528
Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu
165 170 175

GAA AGG CAA CCG GTG ACC AAA AAC ACT TTC AGG CAG TAT CGA GTG CTA 576
Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu
180 185 190

GGA AAA GGG GGC TTC GGG GAG GTC TGT GCC TGC CAG GTT CGG GCC ACG 624
Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr
195 200 205

GGT AAA ATG TAT GCC TGC AAG CGC TTG GAG AAG AAG AGG ATC AAA AAG 672
Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys
210 215 220

AGG AAA GGG GAG TCC ATG GCC CTC AAT GAG AAG CAG ATC CTC GAG AAG 720
Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys
225 230 235 240

GTC AAC AGT CAG TTT GTG GTC AAC CTG GCC TAT GCC TAC GAG ACC AAG 768
Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys
245 250 255

GAT GCA CTG TGC TTG GTC CTG ACC ATC ATG AAT GGG GGT GAC CTG AAG 816

Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys
260 265 270

TTC CAC ATC TAC AAC ATG GGC AAC CCT GGC TTC GAG GAG GAG CGG GCC 864
Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala
275 280 285

TTG TTT TAT GCG GCA GAG ATC CTC TGC GGC TTA GAA GAC CTC CAC CGT 912
Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg
290 295 300

GAG AAC ACC GTC TAC CGA GAT CTG AAA CCT GAA AAC ATC CTG TTA GAT 960
Glu Asn Thr Val Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp
305 310 315 320

GAT TAT GGC CAC ATT AGG ATC TCA GAC CTG GGC TTG GCT GTG AAG ATC 1008
Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile
325 330 335

CCC GAG GGA GAC CTG ATC CGC GGC CGG GTG GGC ACT GTT GGC TAC ATG 1056
Pro Glu Gly Asp Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met
340 345 350

GCC CCC GAA GTC CTG AAC AAC CAG AGG TAC GGC CTG AGC CCC GAC TAC 1104
Ala Pro Glu Val Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr
355 360 365

TGG GGC CTT GGC TGC CTC ATC TAT GAG ATG ATC GAG GGC CAG TCG CCG 1152
Trp Gly Leu Gly Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro
370 375 380

TTC CGC GGC CGT AAG GAG AAG GTG AAG CGG GAG GAG GTG GAC CGC CGG 1200
Phe Arg Gly Arg Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg
385 390 395 400

GTC CTG GAG ACG GAG GAG GTG TAC TCC CAC AAG TTC TCC GAG GAG GCC 1248
Val Leu Glu Thr Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala
405 410 415

AAG TCC ATC TGC AAG ATG CTG CTC ACG AAA GAT GCG AAG CAG AGG CTG 1296
Lys Ser Ile Cys Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu
420 425 430

GGC TGC CAG GAG GAG GGG GCT GCA GAG GTC AAG AGA CAC CCC TTC TTC 1344
Gly Cys Gln Glu Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe
435 440 445

AGG AAC ATG AAC TTC AAG CGC TTA GAA GCC GGG ATG TTG GAC CCT CCC 1392
Arg Asn Met Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro
450 455 460

TTC GTT CCA GAC CCC CGC GCT GTG TAC TGT AAG GAC GTG CTG GAC ATC 1440
Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile
465 470 475 480

GAG CAG TTC TCC ACT GTG AAG GGC GTC AAT CTG GAC CAC ACA GAC GAC 1488
Glu Gln Phe Ser Thr Val Lys Gly Val Asn Leu Asp His Thr Asp Asp
485 490 495

GAC TTC TAC TCC AAG TTC TCC ACG GGC TCT GTG TCC ATC CCA TGG CAA 1536
Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln
500 505 510

AAC GAG ATG ATA GAA ACA GAA TGC TTT AAG GAG CTG AAC GTG TTT GGA 1584
Asn Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly
515 520 525

CCT AAT GGT ACC CTC CCG CCA GAT CTG AAC AGA AAC CAC CCT CCG GAA 1632
Pro Asn Gly Thr Leu Pro Pro Asp Leu Asn Arg Asn His Pro Pro Glu
530 535 540

CCG CCC AAG AAA GGG CTG CTC CAG AGA CTC TTC AAG CGG CAG CAT CAG 1680
Pro Pro Lys Lys Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln
545 550 555 560

AAC AAT TCC AAG AGT TCG CCC AGC TCC AAG ACC AGT TTT AAC CAC CAC 1728
Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His
565 570 575

ATA AAC TCA AAC CAT GTC AGC TCG AAC TCC ACC GGA AGC AGC AGG GAT 1776
Ile Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp
580 585 590

CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG 1824
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
595 600 605

GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG 1872
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
610 615 620

TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG 1920
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
625 630 635 640

ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC 1968
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
645 650 655

ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC 2016
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
660 665 670

CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA 2064
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
675 680 685

GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC 2112
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
690 695 700

AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC 2160
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
705 710 715 720

ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG 2208

Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
725 730 735

CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC 2256
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
740 745 750

GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC 2304
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
755 760 765

ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC 2352
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
770 775 780

CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC 2400
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
785 790 795 800

ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG 2448
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
805 810 815

GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC 2496
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
820 825 830

GAG CTG TAC AAG TAA 2511
Glu Leu Tyr Lys
835

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 836 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg
1 5 10 15
Glu Gly Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu
20 25 30
Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr
35 40 45
Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg
50 55 60
Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr
65 70 75 80
Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu
85 90 95
Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro

```
                100                 105                 110
Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln
            115                 120                 125
Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala
        130                 135                 140
Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu
145                 150                 155                 160
Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu
                    165                 170                 175
Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu
                180                 185                 190
Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr
            195                 200                 205
Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys
        210                 215                 220
Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys
225                 230                 235                 240
Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys
                    245                 250                 255
Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys
                260                 265                 270
Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala
            275                 280                 285
Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg
        290                 295                 300
Glu Asn Thr Val Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp
305                 310                 315                 320
Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile
                    325                 330                 335
Pro Glu Gly Asp Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met
                340                 345                 350
Ala Pro Glu Val Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr
            355                 360                 365
Trp Gly Leu Gly Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro
        370                 375                 380
Phe Arg Gly Arg Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg
385                 390                 395                 400
Val Leu Glu Thr Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala
                    405                 410                 415
Lys Ser Ile Cys Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu
                420                 425                 430
Gly Cys Gln Glu Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe
            435                 440                 445
Arg Asn Met Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro
        450                 455                 460
Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile
465                 470                 475                 480
Glu Gln Phe Ser Thr Val Lys Gly Val Asn Leu Asp His Thr Asp Asp
                    485                 490                 495
Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln
                500                 505                 510
Asn Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly
            515                 520                 525
Pro Asn Gly Thr Leu Pro Pro Asp Leu Asn Arg Asn His Pro Pro Glu
        530                 535                 540
Pro Pro Lys Lys Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln
545                 550                 555                 560
Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His
```

```
                  565                 570                 575
Ile Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp
            580                 585                 590
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
        595                 600                 605
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
    610                 615                 620
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
625                 630                 635                 640
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
                645                 650                 655
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
            660                 665                 670
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
        675                 680                 685
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
    690                 695                 700
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
705                 710                 715                 720
Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
                725                 730                 735
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
            740                 745                 750
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
        755                 760                 765
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
    770                 775                 780
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
785                 790                 795                 800
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
                805                 810                 815
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
            820                 825                 830
Glu Leu Tyr Lys
        835
```

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1893 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1890
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

```
ATG AGC AGA AGC AAG CGT GAC AAC AAT TTT TAT AGT GTA GAG ATT GGA      48
Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly
 1               5                  10                  15

GAT TCT ACA TTC ACA GTC CTG AAA CGA TAT CAG AAT TTA AAA CCT ATA      96
```

Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile
20 25 30

GGC TCA GGA GCT CAA GGA ATA GTA TGC GCA GCT TAT GAT GCC ATT CTT 144
Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu
35 40 45

GAA AGA AAT GTT GCA ATC AAG AAG CTA AGC CGA CCA TTT CAG AAT CAG 192
Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
50 55 60

ACT CAT GCC AAG CGG GCC TAC AGA GAG CTA GTT CTT ATG AAA TGT GTT 240
Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val
65 70 75 80

AAT CAC AAA AAT ATA ATT GGC CTT TTG AAT GTT TTC ACA CCA CAG AAA 288
Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys
85 90 95

TCC CTA GAA GAA TTT CAA GAT GTT TAC ATA GTC ATG GAG CTC ATG GAT 336
Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp
100 105 110

GCA AAT CTT TGC CAA GTG ATT CAG ATG GAG CTA GAT CAT GAA AGA ATG 384
Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met
115 120 125

TCC TAC CTT CTC TAT CAG ATG CTG TGT GGA ATC AAG CAC CTT CAT TCT 432
Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
130 135 140

GCT GGA ATT ATT CAT CGG GAC TTA AAG CCC AGT AAT ATA GTA GTA AAA 480
Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145 150 155 160

TCT GAT TGC ACT TTG AAG ATT CTT GAC TTC GGT CTG GCC AGG ACT GCA 528
Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
165 170 175

GGA ACG AGT TTT ATG ATG ACG CCT TAT GTA GTG ACT CGC TAC TAC AGA 576
Gly Thr Ser Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
180 185 190

GCA CCC GAG GTC ATC CTT GGC ATG GGC TAC AAG GAA AAC GTG GAT TTA 624
Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Val Asp Leu
195 200 205

TGG TCT GTG GGG TGC ATT ATG GGA GAA ATG GTT TGC CAC AAA ATC CTC 672
Trp Ser Val Gly Cys Ile Met Gly Glu Met Val Cys His Lys Ile Leu
210 215 220

TTT CCA GGA AGG GAC TAT ATT GAT CAG TGG AAT AAA GTT ATT GAA CAG 720
Phe Pro Gly Arg Asp Tyr Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
225 230 235 240

CTT GGA ACA CCA TGT CCT GAA TTC ATG AAG AAA CTG CAA CCA ACA GTA 768
Leu Gly Thr Pro Cys Pro Glu Phe Met Lys Lys Leu Gln Pro Thr Val
245 250 255

AGG ACT TAC GTT GAA AAC AGA CCT AAA TAT GCT GGA TAT AGC TTT GAG 816
Arg Thr Tyr Val Glu Asn Arg Pro Lys Tyr Ala Gly Tyr Ser Phe Glu
260 265 270

AAA CTC TTC CCT GAT GTC CTT TTC CCA GCT GAC TCA GAA CAC AAC AAA 864
Lys Leu Phe Pro Asp Val Leu Phe Pro Ala Asp Ser Glu His Asn Lys
275 280 285

CTT AAA GCC AGT CAG GCA AGG GAT TTG TTA TCC AAA ATG CTG GTA ATA 912
Leu Lys Ala Ser Gln Ala Arg Asp Leu Leu Ser Lys Met Leu Val Ile
290 295 300

GAT GCA TCT AAA AGG ATC TCT GTA GAT GAA GCT CTC CAA CAC CCG TAC 960
Asp Ala Ser Lys Arg Ile Ser Val Asp Glu Ala Leu Gln His Pro Tyr
305 310 315 320

ATC AAT GTC TGG TAT GAT CCT TCT GAA GCA GAA GCT CCA CCA CCA AAG 1008
Ile Asn Val Trp Tyr Asp Pro Ser Glu Ala Glu Ala Pro Pro Pro Lys
325 330 335

ATC CCT GAC AAG CAG TTA GAT GAA AGG GAA CAC ACA ATA GAA GAG TGG 1056
Ile Pro Asp Lys Gln Leu Asp Glu Arg Glu His Thr Ile Glu Glu Trp
340 345 350

AAA GAA TTG ATA TAT AAG GAA GTT ATG GAC TTG GAG GAG AGA ACC AAG 1104
Lys Glu Leu Ile Tyr Lys Glu Val Met Asp Leu Glu Glu Arg Thr Lys
355 360 365

AAT GGA GTT ATA CGG GGG CAG CCC TCT CCT TTA GCA CAG GTG CAG CAG 1152
Asn Gly Val Ile Arg Gly Gln Pro Ser Pro Leu Ala Gln Val Gln Gln
370 375 380

TGG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC 1200
Trp Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
385 390 395 400

ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC 1248
Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
405 410 415

CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC 1296
His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
420 425 430

AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC 1344
Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro
435 440 445

TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC 1392
Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser
450 455 460

CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG 1440
Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
465 470 475 480

CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC 1488

```
Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
                485                 490                 495

AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG     1536
Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val
            500                 505                 510

AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC     1584
Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
        515                 520                 525

CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC     1632
Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
    530                 535                 540

ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC     1680
Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
545                 550                 555                 560

CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG     1728
His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
                565                 570                 575

AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC     1776
Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
            580                 585                 590

CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT     1824
Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
        595                 600                 605

CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC     1872
His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
    610                 615                 620

ATG GAC GAG CTG TAC AAG TAA                                          1893
Met Asp Glu Leu Tyr Lys
625                 630
```

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 630 amino acids
  (B) TYPE: amino acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```
Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly
 1               5                  10                  15
Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile
            20                  25                  30
Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu
```

            35   40   45
Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
        50   55   60
Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val
65   70   75   80
Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys
                85   90   95
Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp
            100   105   110
Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met
        115   120   125
Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
    130   135   140
Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145   150   155   160
Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
                165   170   175
Gly Thr Ser Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
            180   185   190
Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Val Asp Leu
        195   200   205
Trp Ser Val Gly Cys Ile Met Gly Glu Met Val Cys His Lys Ile Leu
    210   215   220
Phe Pro Gly Arg Asp Tyr Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
225   230   235   240
Leu Gly Thr Pro Cys Pro Glu Phe Met Lys Lys Leu Gln Pro Thr Val
                245   250   255
Arg Thr Tyr Val Glu Asn Arg Pro Lys Tyr Ala Gly Tyr Ser Phe Glu
            260   265   270
Lys Leu Phe Pro Asp Val Leu Phe Pro Ala Asp Ser Glu His Asn Lys
        275   280   285
Leu Lys Ala Ser Gln Ala Arg Asp Leu Leu Ser Lys Met Leu Val Ile
    290   295   300
Asp Ala Ser Lys Arg Ile Ser Val Asp Glu Ala Leu Gln His Pro Tyr
305   310   315   320
Ile Asn Val Trp Tyr Asp Pro Ser Glu Ala Glu Ala Pro Pro Pro Lys
                325   330   335
Ile Pro Asp Lys Gln Leu Asp Glu Arg Glu His Thr Ile Glu Glu Trp
            340   345   350
Lys Glu Leu Ile Tyr Lys Glu Val Met Asp Leu Glu Glu Arg Thr Lys
        355   360   365
Asn Gly Val Ile Arg Gly Gln Pro Ser Pro Leu Ala Gln Val Gln Gln
    370   375   380
Trp Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
385   390   395   400
Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
                405   410   415
His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
            420   425   430
Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro
        435   440   445
Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser
    450   455   460
Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
465   470   475   480
Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
                485   490   495
Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val

```
            500                 505                 510
Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
        515                 520                 525
Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
    530                 535                 540
Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
545                 550                 555                 560
His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
                565                 570                 575
Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
            580                 585                 590
Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
        595                 600                 605
His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
    610                 615                 620
Met Asp Glu Leu Tyr Lys
625                 630
```

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1821 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1818
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```
ATG TCT CAG GAG AGG CCC ACG TTC TAC CGG CAG GAG CTG AAC AAG ACA       48
Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr
 1               5                  10                  15

ATC TGG GAG GTG CCC GAG CGT TAC CAG AAC CTG TCT CCA GTG GGC TCT       96
Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser
            20                  25                  30

GGC GCC TAT GGC TCT GTG TGT GCT GCT TTT GAC ACA AAA ACG GGG TTA      144
Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu
        35                  40                  45

CGT GTG GCA GTG AAG AAG CTC TCC AGA CCA TTT CAG TCC ATC ATT CAT      192
Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His
    50                  55                  60

GCG AAA AGA ACC TAC AGA GAA CTG CGG TTA CTT AAA CAT ATG AAA CAT      240
Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His
65                  70                  75                  80

GAA AAT GTG ATT GGT CTG TTG GAC GTT TTT ACA CCT GCA AGG TCT CTG      288
Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu
                85                  90                  95
```

```
GAG GAA TTC AAT GAT GTG TAT CTG GTG ACC CAT CTC ATG GGG GCA GAT      336
Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp
            100                 105                 110

CTG AAC AAC ATT GTG AAA TGT CAG AAG CTT ACA GAT GAC CAT GTT CAG      384
Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln
        115                 120                 125

TTC CTT ATC TAC CAA ATT CTC CGA GGT CTA AAG TAT ATA CAT TCA GCT      432
Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala
    130                 135                 140

GAC ATA ATT CAC AGG GAC CTA AAA CCT AGT AAT CTA GCT GTG AAT GAA      480
Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu
145                 150                 155                 160

GAC TGT GAG CTG AAG ATT CTG GAT TTT GGA CTG GCT CGG CAC ACA GAT      528
Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp
                165                 170                 175

GAT GAA ATG ACA GGC TAC GTG GCC ACT AGG TGG TAC AGG GCT CCT GAG      576
Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu
            180                 185                 190

ATC ATG CTG AAC TGG ATG CAT TAC AAC CAG ACA GTT GAT ATT TGG TCA      624
Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser
        195                 200                 205

GTG GGA TGC ATA ATG GCC GAG CTG TTG ACT GGA AGA ACA TTG TTT CCT      672
Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro
    210                 215                 220

GGT ACA GAC CAT ATT GAT CAG TTG AAG CTC ATT TTA AGA CTC GTT GGA      720
Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly
225                 230                 235                 240

ACC CCA GGG GCT GAG CTT TTG AAG AAA ATC TCC TCA GAG TCT GCA AGA      768
Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg
                245                 250                 255

AAC TAT ATT CAG TCT TTG ACT CAG ATG CCG AAG ATG AAC TTT GCG AAT      816
Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn
            260                 265                 270

GTA TTT ATT GGT GCC AAT CCC CTG GCT GTC GAC TTG CTG GAG AAG ATG      864
Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met
        275                 280                 285

CTT GTA TTG GAC TCA GAT AAG AGA ATT ACA GCG GCC CAA GCC CTT GCA      912
Leu Val Leu Asp Ser Asp Lys Arg Ile Thr Ala Ala Gln Ala Leu Ala
    290                 295                 300

CAT GCC TAC TTT GCT CAG TAC CAC GAT CCT GAT GAT GAA CCA GTG GCC      960
His Ala Tyr Phe Ala Gln Tyr His Asp Pro Asp Asp Glu Pro Val Ala
305                 310                 315                 320

GAT CCT TAT GAT CAG TCC TTT GAA AGC AGG GAC CTC CTT ATA GAT GAG     1008
```

```
Asp Pro Tyr Asp Gln Ser Phe Glu Ser Arg Asp Leu Leu Ile Asp Glu
                325                 330                 335

TGG AAA AGC CTG ACC TAT GAT GAA GTC ATC AGC TTT GTG CCA CCA CCC     1056
Trp Lys Ser Leu Thr Tyr Asp Glu Val Ile Ser Phe Val Pro Pro Pro
            340                 345                 350

CTT GAC CAA GAA GAG ATG GAG TCC GAG GAT CCA CCG GTC GCC ACC ATG     1104
Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met
        355                 360                 365

GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC     1152
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
    370                 375                 380

GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG     1200
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
385                 390                 395                 400

GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC     1248
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
                405                 410                 415

ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG     1296
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
            420                 425                 430

ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG     1344
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
        435                 440                 445

CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC     1392
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
    450                 455                 460

ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG     1440
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
465                 470                 475                 480

AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC     1488
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
                485                 490                 495

GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC     1536
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
            500                 505                 510

TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC     1584
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
        515                 520                 525

ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG     1632
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
    530                 535                 540

CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC     1680
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
545                 550                 555                 560
```

```
GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC      1728
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
                565                 570                 575

AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG      1776
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
            580                 585                 590

ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA          1821
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
        595                 600                 605
```

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 606 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```
Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr
 1               5                  10                  15
Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser
            20                  25                  30
Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu
        35                  40                  45
Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His
    50                  55                  60
Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His
65                  70                  75                  80
Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu
                85                  90                  95
Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp
            100                 105                 110
Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln
        115                 120                 125
Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala
    130                 135                 140
Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu
145                 150                 155                 160
Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp
                165                 170                 175
Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu
            180                 185                 190
Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser
        195                 200                 205
Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro
    210                 215                 220
Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly
225                 230                 235                 240
Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg
```

```
                    245                 250                 255
Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn
                260                 265                 270
Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met
            275                 280                 285
Leu Val Leu Asp Ser Asp Lys Arg Ile Thr Ala Ala Gln Ala Leu Ala
        290                 295                 300
His Ala Tyr Phe Ala Gln Tyr His Asp Pro Asp Asp Glu Pro Val Ala
305                 310                 315                 320
Asp Pro Tyr Asp Gln Ser Phe Glu Ser Arg Asp Leu Leu Ile Asp Glu
                325                 330                 335
Trp Lys Ser Leu Thr Tyr Asp Glu Val Ile Ser Phe Val Pro Pro Pro
            340                 345                 350
Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met
        355                 360                 365
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
    370                 375                 380
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
385                 390                 395                 400
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
                405                 410                 415
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
            420                 425                 430
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
        435                 440                 445
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
    450                 455                 460
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
465                 470                 475                 480
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
                485                 490                 495
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
            500                 505                 510
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
        515                 520                 525
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
    530                 535                 540
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
545                 550                 555                 560
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
                565                 570                 575
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
            580                 585                 590
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
        595                 600                 605
```

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2913 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2910
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

ATG AGT GCT GAG GGG TAC CAG TAC AGA GCG CTG TAT GAT TAT AAA AAG 48
Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr Asp Tyr Lys Lys
1 5 10 15

GAA AGA GAA GAA GAT ATT GAC TTG CAC TTG GGT GAC ATA TTG ACT GTG 96
Glu Arg Glu Glu Asp Ile Asp Leu His Leu Gly Asp Ile Leu Thr Val
20 25 30

AAT AAA GGG TCC TTA GTA GCT CTT GGA TTC AGT GAT GGA CAG GAA GCC 144
Asn Lys Gly Ser Leu Val Ala Leu Gly Phe Ser Asp Gly Gln Glu Ala
35 40 45

AGG CCT GAA GAA ATT GGC TGG TTA AAT GGC TAT AAT GAA ACC ACA GGG 192
Arg Pro Glu Glu Ile Gly Trp Leu Asn Gly Tyr Asn Glu Thr Thr Gly
50 55 60

GAA AGG GGG GAC TTT CCG GGA ACT TAC GTA GAA TAT ATT GGA AGG AAA 240
Glu Arg Gly Asp Phe Pro Gly Thr Tyr Val Glu Tyr Ile Gly Arg Lys
65 70 75 80

AAA ATC TCG CCT CCC ACA CCA AAG CCC CGG CCA CCT CGG CCT CTT CCT 288
Lys Ile Ser Pro Pro Thr Pro Lys Pro Arg Pro Pro Arg Pro Leu Pro
85 90 95

GTT GCA CCA GGT TCT TCG AAA ACT GAA GCA GAT GTT GAA CAA CAA GCT 336
Val Ala Pro Gly Ser Ser Lys Thr Glu Ala Asp Val Glu Gln Gln Ala
100 105 110

TTG ACT CTC CCG GAT CTT GCA GAG CAG TTT GCC CCT CCT GAC ATT GCC 384
Leu Thr Leu Pro Asp Leu Ala Glu Gln Phe Ala Pro Pro Asp Ile Ala
115 120 125

CCG CCT CTT CTT ATC AAG CTC GTG GAA GCC ATT GAA AAG AAA GGT CTG 432
Pro Pro Leu Leu Ile Lys Leu Val Glu Ala Ile Glu Lys Lys Gly Leu
130 135 140

GAA TGT TCA ACT CTA TAC AGA ACA CAG AGC TCC AGC AAC CTG GCA GAA 480
Glu Cys Ser Thr Leu Tyr Arg Thr Gln Ser Ser Ser Asn Leu Ala Glu
145 150 155 160

TTA CGA CAG CTT CTT GAT TGT GAT ACA CCC TCC GTG GAC TTG GAA ATG 528
Leu Arg Gln Leu Leu Asp Cys Asp Thr Pro Ser Val Asp Leu Glu Met
165 170 175

ATC GAT GTG CAC GTT TTG GCT GAC GCT TTC AAA CGC TAT CTC CTG GAC 576
Ile Asp Val His Val Leu Ala Asp Ala Phe Lys Arg Tyr Leu Leu Asp
180 185 190

TTA CCA AAT CCT GTC ATT CCA GCA GCC GTT TAC AGT GAA ATG ATT TCT 624
Leu Pro Asn Pro Val Ile Pro Ala Ala Val Tyr Ser Glu Met Ile Ser
195 200 205

TTA GCT CCA GAA GTA CAA AGC TCC GAA GAA TAT ATT CAG CTA TTG AAG 672

```
Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile Gln Leu Leu Lys
    210                 215                 220

AAG CTT ATT AGG TCG CCT AGC ATA CCT CAT CAG TAT TGG CTT ACG CTT      720
Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr Trp Leu Thr Leu
225                 230                 235                 240

CAG TAT TTG TTA AAA CAT TTC TTC AAG CTC TCT CAA ACC TCC AGC AAA      768
Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln Thr Ser Ser Lys
                245                 250                 255

AAT CTG TTG AAT GCA AGA GTA CTC TCT GAA ATT TTC AGC CCT ATG CTT      816
Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe Ser Pro Met Leu
            260                 265                 270

TTC AGA TTC TCA GCA GCC AGC TCT GAT AAT ACT GAA AAC CTC ATA AAA      864
Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu Asn Leu Ile Lys
        275                 280                 285

GTT ATA GAA ATT TTA ATC TCA ACT GAA TGG AAT GAA CGA CAG CCT GCA      912
Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu Arg Gln Pro Ala
    290                 295                 300

CCA GCA CTG CCT CCT AAA CCA CCA AAA CCT ACT ACT GTA GCC AAC AAC      960
Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr Val Ala Asn Asn
305                 310                 315                 320

GGT ATG AAT AAC AAT ATG TCC TTA CAA AAT GCT GAA TGG TAC TGG GGA     1008
Gly Met Asn Asn Asn Met Ser Leu Gln Asn Ala Glu Trp Tyr Trp Gly
                325                 330                 335

GAT ATC TCG AGG GAA GAA GTG AAT GAA AAA CTT CGA GAT ACA GCA GAC     1056
Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg Asp Thr Ala Asp
            340                 345                 350

GGG ACC TTT TTG GTA CGA GAT GCG TCT ACT AAA ATG CAT GGT GAT TAT     1104
Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met His Gly Asp Tyr
        355                 360                 365

ACT CTT ACA CTA AGG AAA GGG GGA AAT AAC AAA TTA ATC AAA ATA TTT     1152
Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu Ile Lys Ile Phe
    370                 375                 380

CAT CGA GAT GGG AAA TAT GGC TTC TCT GAC CCA TTA ACC TTC AGT TCT     1200
His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser
385                 390                 395                 400

GTG GTT GAA TTA ATA AAC CAC TAC CGG AAT GAA TCT CTA GCT CAG TAT     1248
Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr
                405                 410                 415

AAT CCC AAA TTG GAT GTG AAA TTA CTT TAT CCA GTA TCC AAA TAC CAA     1296
Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln
            420                 425                 430

CAG GAT CAA GTT GTC AAA GAA GAT AAT ATT GAA GCT GTA GGG AAA AAA     1344
Gln Asp Gln Val Val Lys Glu Asp Asn Ile Glu Ala Val Gly Lys Lys
        435                 440                 445
```

TTA CAT GAA TAT AAC ACT CAG TTT CAA GAA AAA AGT CGA GAA TAT GAT 1392
Leu His Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser Arg Glu Tyr Asp
450 455 460

AGA TTA TAT GAA GAA TAT ACC CGC ACA TCC CAG GAA ATC CAA ATG AAA 1440
Arg Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu Ile Gln Met Lys
465 470 475 480

AGG ACA GCT ATT GAA GCA TTT AAT GAA ACC ATA AAA ATA TTT GAA GAA 1488
Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys Ile Phe Glu Glu
485 490 495

CAG TGC CAG ACC CAA GAG CGG TAC AGC AAA GAA TAC ATA GAA AAG TTT 1536
Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr Ile Glu Lys Phe
500 505 510

AAA CGT GAA GGC AAT GAG AAA GAA ATA CAA AGG ATT ATG CAT AAT TAT 1584
Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile Met His Asn Tyr
515 520 525

GAT AAG TTG AAG TCT CGA ATC AGT GAA ATT ATT GAC AGT AGA AGA AGA 1632
Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp Ser Arg Arg Arg
530 535 540

TTG GAA GAA GAC TTG AAG AAG CAG GCA GCT GAG TAT CGA GAA ATT GAC 1680
Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu Tyr Arg Glu Ile Asp
545 550 555 560

AAA CGT ATG AAC AGC ATT AAA CCA GAC CTT ATC CAG CTG AGA AAG ACG 1728
Lys Arg Met Asn Ser Ile Lys Pro Asp Leu Ile Gln Leu Arg Lys Thr
565 570 575

AGA GAC CAA TAC TTG ATG TGG TTG ACT CAA AAA GGT GTT CGG CAA AAG 1776
Arg Asp Gln Tyr Leu Met Trp Leu Thr Gln Lys Gly Val Arg Gln Lys
580 585 590

AAG TTG AAC GAG TGG TTG GGC AAT GAA AAC ACT GAA GAC CAA TAT TCA 1824
Lys Leu Asn Glu Trp Leu Gly Asn Glu Asn Thr Glu Asp Gln Tyr Ser
595 600 605

CTG GTG GAA GAT GAT GAA GAT TTG CCC CAT CAT GAT GAG AAG ACA TGG 1872
Leu Val Glu Asp Asp Glu Asp Leu Pro His His Asp Glu Lys Thr Trp
610 615 620

AAT GTT GGA AGC AGC AAC CGA AAC AAA GCT GAA AAC CTG TTG CGA GGG 1920
Asn Val Gly Ser Ser Asn Arg Asn Lys Ala Glu Asn Leu Leu Arg Gly
625 630 635 640

AAG CGA GAT GGC ACT TTT CTT GTC CGG GAG AGC AGT AAA CAG GGC TGC 1968
Lys Arg Asp Gly Thr Phe Leu Val Arg Glu Ser Ser Lys Gln Gly Cys
645 650 655

TAT GCC TGC TCT GTA GTG GTG GAC GGC GAA GTA AAG CAT TGT GTC ATA 2016
Tyr Ala Cys Ser Val Val Val Asp Gly Glu Val Lys His Cys Val Ile
660 665 670

AAC AAA ACA GCA ACT GGC TAT GGC TTT GCC GAG CCC TAT AAC TTG TAC 2064

```
Asn Lys Thr Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr
        675                 680                 685

AGC TCT CTG AAA GAA CTG GTG CTA CAT TAC CAA CAC ACC TCC CTT GTG     2112
Ser Ser Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val
    690                 695                 700

CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC CCA GTA TAT GCA     2160
Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala
705                 710                 715                 720

CAG CAG AGG CGA CAG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC     2208
Gln Gln Arg Arg Gln Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly
                725                 730                 735

GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC     2256
Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly
            740                 745                 750

GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT     2304
Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp
        755                 760                 765

GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG     2352
Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys
    770                 775                 780

CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG     2400
Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val
785                 790                 795                 800

CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC     2448
Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe
                805                 810                 815

AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC     2496
Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe
            820                 825                 830

AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC     2544
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
        835                 840                 845

GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG     2592
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
    850                 855                 860

GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC     2640
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
865                 870                 875                 880

AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC     2688
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
                885                 890                 895

TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC     2736
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
            900                 905                 910
```

```
CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC     2784
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
        915                 920                 925

GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC     2832
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
    930                 935                 940

GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG     2880
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
945                 950                 955                 960

ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA                          2913
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
                965                 970
```

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 970 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr Asp Tyr Lys Lys
 1               5                  10                  15
Glu Arg Glu Glu Asp Ile Asp Leu His Leu Gly Asp Ile Leu Thr Val
            20                  25                  30
Asn Lys Gly Ser Leu Val Ala Leu Gly Phe Ser Asp Gly Gln Glu Ala
        35                  40                  45
Arg Pro Glu Glu Ile Gly Trp Leu Asn Gly Tyr Asn Glu Thr Thr Gly
    50                  55                  60
Glu Arg Gly Asp Phe Pro Gly Thr Tyr Val Glu Tyr Ile Gly Arg Lys
65                  70                  75                  80
Lys Ile Ser Pro Pro Thr Pro Lys Pro Arg Pro Pro Arg Pro Leu Pro
                85                  90                  95
Val Ala Pro Gly Ser Ser Lys Thr Glu Ala Asp Val Glu Gln Gln Ala
            100                 105                 110
Leu Thr Leu Pro Asp Leu Ala Glu Gln Phe Ala Pro Pro Asp Ile Ala
        115                 120                 125
Pro Pro Leu Leu Ile Lys Leu Val Glu Ala Ile Glu Lys Lys Gly Leu
    130                 135                 140
Glu Cys Ser Thr Leu Tyr Arg Thr Gln Ser Ser Ser Asn Leu Ala Glu
145                 150                 155                 160
Leu Arg Gln Leu Leu Asp Cys Asp Thr Pro Ser Val Asp Leu Glu Met
                165                 170                 175
Ile Asp Val His Val Leu Ala Asp Ala Phe Lys Arg Tyr Leu Leu Asp
            180                 185                 190
Leu Pro Asn Pro Val Ile Pro Ala Ala Val Tyr Ser Glu Met Ile Ser
        195                 200                 205
Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile Gln Leu Leu Lys
```

210 215 220
Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr Trp Leu Thr Leu
225 230 235 240
Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln Thr Ser Ser Lys
245 250 255
Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe Ser Pro Met Leu
260 265 270
Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu Asn Leu Ile Lys
275 280 285
Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu Arg Gln Pro Ala
290 295 300
Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr Val Ala Asn Asn
305 310 315 320
Gly Met Asn Asn Asn Met Ser Leu Gln Asn Ala Glu Trp Tyr Trp Gly
325 330 335
Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg Asp Thr Ala Asp
340 345 350
Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met His Gly Asp Tyr
355 360 365
Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu Ile Lys Ile Phe
370 375 380
His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser
385 390 395 400
Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr
405 410 415
Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln
420 425 430
Gln Asp Gln Val Val Lys Glu Asp Asn Ile Glu Ala Val Gly Lys Lys
435 440 445
Leu His Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser Arg Glu Tyr Asp
450 455 460
Arg Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu Ile Gln Met Lys
465 470 475 480
Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys Ile Phe Glu Glu
485 490 495
Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr Ile Glu Lys Phe
500 505 510
Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile Met His Asn Tyr
515 520 525
Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp Ser Arg Arg Arg
530 535 540
Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu Tyr Arg Glu Ile Asp
545 550 555 560
Lys Arg Met Asn Ser Ile Lys Pro Asp Leu Ile Gln Leu Arg Lys Thr
565 570 575
Arg Asp Gln Tyr Leu Met Trp Leu Thr Gln Lys Gly Val Arg Gln Lys
580 585 590
Lys Leu Asn Glu Trp Leu Gly Asn Glu Asn Thr Glu Asp Gln Tyr Ser
595 600 605
Leu Val Glu Asp Asp Glu Asp Leu Pro His His Asp Glu Lys Thr Trp
610 615 620
Asn Val Gly Ser Ser Asn Arg Asn Lys Ala Glu Asn Leu Leu Arg Gly
625 630 635 640
Lys Arg Asp Gly Thr Phe Leu Val Arg Glu Ser Ser Lys Gln Gly Cys
645 650 655
Tyr Ala Cys Ser Val Val Val Asp Gly Glu Val Lys His Cys Val Ile
660 665 670
Asn Lys Thr Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr

675 680 685
Ser Ser Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val
690 695 700
Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala
705 710 715 720
Gln Gln Arg Arg Gln Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly
725 730 735
Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly
740 745 750
Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp
755 760 765
Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys
770 775 780
Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val
785 790 795 800
Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe
805 810 815
Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe
820 825 830
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
835 840 845
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
850 855 860
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
865 870 875 880
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
885 890 895
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
900 905 910
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
915 920 925
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
930 935 940
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
945 950 955 960
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
965 970

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1788 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1785
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

ATG GGC AAC GCC GCC GCC GCC AAG AAG GGC AGC GAG CAG GAG AGC GTG 48
Met Gly Asn Ala Ala Ala Ala Lys Lys Gly Ser Glu Gln Glu Ser Val
1 5 10 15

AAA GAG TTC CTA GCC AAA GCC AAG GAA GAT TTC CTG AAA AAA TGG GAA 96
Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu
20 25 30

GAC CCC TCT CAG AAT ACA GCC CAG TTG GAT CAG TTT GAT AGA ATC AAG 144
Asp Pro Ser Gln Asn Thr Ala Gln Leu Asp Gln Phe Asp Arg Ile Lys
35 40 45

ACC CTT GGC ACC GGC TCC TTT GGG CGA GTG ATG CTG GTG AAG CAC AAG 192
Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys
50 55 60

GAG AGT GGG AAC CAC TAC GCC ATG AAG ATC TTA GAC AAG CAG AAG GTG 240
Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val
65 70 75 80

GTG AAG CTA AAG CAG ATC GAG CAC ACT CTG AAT GAG AAG CGC ATC CTG 288
Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu
85 90 95

CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA TTC TCC TTC AAG 336
Gln Ala Val Asn Phe Pro Phe Leu Val Lys Leu Glu Phe Ser Phe Lys
100 105 110

GAC AAC TCA AAC CTG TAC ATG GTC ATG GAG TAT GTA GCT GGT GGC GAG 384
Asp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu
115 120 125

ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGC GAG CCC CAT GCC 432
Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala
130 135 140

CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC 480
Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser
145 150 155 160

CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC 528
Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp
165 170 175

CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576
Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val
180 185 190

AAA GGC CGT ACT TGG ACC TTG TGT GGG ACC CCT GAG TAC TTG GCC CCC 624
Lys Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro
195 200 205

GAG ATT ATC CTG AGC AAA GGC TAC AAC AAG GCT GTG GAC TGG TGG GCT 672
Glu Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp Ala
210 215 220

CTC GGA GTC CTC ATC TAC GAG ATG GCT GCT GGT TAC CCA CCC TTC TTC 720
Leu Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro Phe Phe
225 230 235 240

GCT GAC CAG CCT ATC CAG ATC TAT GAG AAA ATC GTC TCT GGG AAG GTG 768

```
Ala Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser Gly Lys Val
                245                 250                 255

CGG TTC CCA TCC CAC TTC AGC TCT GAC TTG AAG GAC CTG CTG CGG AAC      816
Arg Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp Leu Leu Arg Asn
            260                 265                 270

CTT CTG CAA GTG GAT CTA ACC AAG CGC TTT GGA AAC CTC AAG GAC GGG      864
Leu Leu Gln Val Asp Leu Thr Lys Arg Phe Gly Asn Leu Lys Asp Gly
        275                 280                 285

GTC AAT GAC ATC AAG AAC CAC AAG TGG TTT GCC ACG ACT GAC TGG ATT      912
Val Asn Asp Ile Lys Asn His Lys Trp Phe Ala Thr Thr Asp Trp Ile
    290                 295                 300

GCC ATC TAT CAG AGA AAG GTG GAA GCT CCC TTC ATA CCA AAG TTT AAA      960
Ala Ile Tyr Gln Arg Lys Val Glu Ala Pro Phe Ile Pro Lys Phe Lys
305                 310                 315                 320

GGC CCT GGG GAC ACG AGT AAC TTT GAC GAC TAT GAG GAG GAA GAG ATC     1008
Gly Pro Gly Asp Thr Ser Asn Phe Asp Asp Tyr Glu Glu Glu Glu Ile
                325                 330                 335

CGG GTC TCC ATC AAT GAG AAG TGT GGC AAG GAG TTT ACT GAG TTT GGG     1056
Arg Val Ser Ile Asn Glu Lys Cys Gly Lys Glu Phe Thr Glu Phe Gly
            340                 345                 350

CGC GCC ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA ATT     1104
Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile
        355                 360                 365

CTT GTT GAA TTA GAT GGC GAT GTT AAT GGG CAA AAA TTC TCT GTT AGT     1152
Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val Ser
    370                 375                 380

GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA AAA CTT ACC CTT AAA TTT     1200
Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe
385                 390                 395                 400

ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT GTC ACT     1248
Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr
                405                 410                 415

ACT CTC ACT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG     1296
Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met
            420                 425                 430

AAA CAG CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG     1344
Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln
        435                 440                 445

GAA AGA ACT ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT     1392
Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala
    450                 455                 460

GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA     1440
Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys
465                 470                 475                 480
```

GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA 1488
Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu
485 490 495

TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG 1536
Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys
500 505 510

AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA 1584
Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly
515 520 525

AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT 1632
Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp
530 535 540

GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC 1680
Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala
545 550 555 560

CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG 1728
Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu
565 570 575

TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA 1776
Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys
580 585 590

CCT CAG GAG TAA 1788
Pro Gln Glu
595

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 595 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Gly Asn Ala Ala Ala Ala Lys Lys Gly Ser Glu Gln Glu Ser Val
1 5 10 15
Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu
20 25 30
Asp Pro Ser Gln Asn Thr Ala Gln Leu Asp Gln Phe Asp Arg Ile Lys
35 40 45
Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys
50 55 60
Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val
65 70 75 80
Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu

85 90 95
Gln Ala Val Asn Phe Pro Phe Leu Val Lys Leu Glu Phe Ser Phe Lys
100 105 110
Asp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu
115 120 125
Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala
130 135 140
Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser
145 150 155 160
Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp
165 170 175
Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val
180 185 190
Lys Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro
195 200 205
Glu Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp Ala
210 215 220
Leu Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro Phe Phe
225 230 235 240
Ala Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser Gly Lys Val
245 250 255
Arg Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp Leu Leu Arg Asn
260 265 270
Leu Leu Gln Val Asp Leu Thr Lys Arg Phe Gly Asn Leu Lys Asp Gly
275 280 285
Val Asn Asp Ile Lys Asn His Lys Trp Phe Ala Thr Thr Asp Trp Ile
290 295 300
Ala Ile Tyr Gln Arg Lys Val Glu Ala Pro Phe Ile Pro Lys Phe Lys
305 310 315 320
Gly Pro Gly Asp Thr Ser Asn Phe Asp Asp Tyr Glu Glu Glu Glu Ile
325 330 335
Arg Val Ser Ile Asn Glu Lys Cys Gly Lys Glu Phe Thr Glu Phe Gly
340 345 350
Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile
355 360 365
Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val Ser
370 375 380
Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe
385 390 395 400
Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr
405 410 415
Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met
420 425 430
Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln
435 440 445
Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala
450 455 460
Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys
465 470 475 480
Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu
485 490 495
Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys
500 505 510
Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly
515 520 525
Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp
530 535 540
Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala

```
545                 550                 555                 560
Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu
                565                 570                 575
Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys
            580                 585                 590
Pro Gln Glu
        595
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 2181 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

  (A) NAME/KEY: Coding Sequence
  (B) LOCATION: 1...2178
  (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
ATG AGC GAC GTG GCT ATT GTG AAG GAG GGT TGG CTG CAC AAA CGA GGG       48
Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly
 1               5                  10                  15

GAG TAC ATC AAG ACC TGG CGG CCA CGC TAC TTC CTC CTC AAG AAT GAT       96
Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp
            20                  25                  30

GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT      144
Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg
        35                  40                  45

GAG GCT CCC CTC AAC AAC TTC TCT GTG GCG CAG TGC CAG CTG ATG AAG      192
Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys
    50                  55                  60

ACG GAG CGG CCC CGG CCC AAC ACC TTC ATC ATC CGC TGC CTG CAG TGG      240
Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp
65                  70                  75                  80

ACC ACT GTC ATC GAA CGC ACC TTC CAT GTG GAG ACT CCT GAG GAG CGG      288
Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg
                85                  90                  95

GAG GAG TGG ACA ACC GCC ATC CAG ACT GTG GCT GAC GGC CTC AAG AAG      336
Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys
            100                 105                 110

CAG GAG GAG GAG GAG ATG GAC TTC CGG TCG GGC TCA CCC AGT GAC AAC      384
Gln Glu Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn
        115                 120                 125

TCA GGG GCT GAA GAG ATG GAG GTG TCC CTG GCC AAG CCC AAG CAC CGC      432
```

Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg
130 135 140

GTG ACC ATG AAC GAG TTT GAG TAC CTG AAG CTG CTG GGC AAG GGC ACT 480
Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr
145 150 155 160

TTC GGC AAG GTG ATC CTG GTG AAG GAG AAG GCC ACA GGC CGC TAC TAC 528
Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr
165 170 175

GCC ATG AAG ATC CTC AAG AAG GAA GTC ATC GTG GCC AAG GAC GAG GTG 576
Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val
180 185 190

GCC CAC ACA CTC ACC GAG AAC CGC GTC CTG CAG AAC TCC AGG CAC CCC 624
Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro
195 200 205

TTC CTC ACA GCC CTG AAG TAC TCT TTC CAG ACC CAC GAC CGC CTC TGC 672
Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys
210 215 220

TTT GTC ATG GAG TAC GCC AAC GGG GGC GAG CTG TTC TTC CAC CTG TCC 720
Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser
225 230 235 240

CGG GAA CGT GTG TTC TCC GAG GAC CGG GCC CGC TTC TAT GGC GCT GAG 768
Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu
245 250 255

ATT GTG TCA GCC CTG GAC TAC CTG CAC TCG GAG AAG AAC GTG GTG TAC 816
Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr
260 265 270

CGG GAC CTC AAG CTG GAG AAC CTC ATG CTG GAC AAG GAC GGG CAC ATT 864
Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile
275 280 285

AAG ATC ACA GAC TTC GGG CTG TGC AAG GAG GGG ATC AAG GAC GGT GCC 912
Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala
290 295 300

ACC ATG AAG ACC TTT TGC GGC ACA CCT GAG TAC CTG GCC CCC GAG GTG 960
Thr Met Lys Thr Phe Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu Val
305 310 315 320

CTG GAG GAC AAT GAC TAC GGC CGT GCA GTG GAC TGG TGG GGG CTG GGC 1008
Leu Glu Asp Asn Asp Tyr Gly Arg Ala Val Asp Trp Trp Gly Leu Gly
325 330 335

GTG GTC ATG TAC GAG ATG ATG TGC GGT CGC CTG CCC TTC TAC AAC CAG 1056
Val Val Met Tyr Glu Met Met Cys Gly Arg Leu Pro Phe Tyr Asn Gln
340 345 350

GAC CAT GAG AAG CTT TTT GAG CTC ATC CTC ATG GAG GAG ATC CGC TTC 1104
Asp His Glu Lys Leu Phe Glu Leu Ile Leu Met Glu Glu Ile Arg Phe
355 360 365

CCG CGC ACG CTT GGT CCC GAG GCC AAG TCC TTG CTT TCA GGG CTG CTC 1152
Pro Arg Thr Leu Gly Pro Glu Ala Lys Ser Leu Leu Ser Gly Leu Leu
370 375 380

AAG AAG GAC CCC AAG CAG AGG CTT GGC GGG GGC TCC GAG GAC GCC AAG 1200
Lys Lys Asp Pro Lys Gln Arg Leu Gly Gly Gly Ser Glu Asp Ala Lys
385 390 395 400

GAG ATC ATG CAG CAT CGC TTC TTT GCC GGT ATC GTG TGG CAG CAC GTG 1248
Glu Ile Met Gln His Arg Phe Phe Ala Gly Ile Val Trp Gln His Val
405 410 415

TAC GAG AAG AAG CTC AGC CCA CCC TTC AAG CCC CAG GTC ACG TCG GAG 1296
Tyr Glu Lys Lys Leu Ser Pro Pro Phe Lys Pro Gln Val Thr Ser Glu
420 425 430

ACT GAC ACC AGG TAT TTT GAT GAG GAG TTC ACG GCC CAG ATG ATC ACC 1344
Thr Asp Thr Arg Tyr Phe Asp Glu Glu Phe Thr Ala Gln Met Ile Thr
435 440 445

ATC ACA CCA CCT GAC CAA GAT GAC AGC ATG GAG TGT GTG GAC AGC GAG 1392
Ile Thr Pro Pro Asp Gln Asp Asp Ser Met Glu Cys Val Asp Ser Glu
450 455 460

CGC AGG CCC CAC TTC CCC CAG TTC TCC TAC TCG GCC AGC AGC ACG GCC 1440
Arg Arg Pro His Phe Pro Gln Phe Ser Tyr Ser Ala Ser Ser Thr Ala
465 470 475 480

TCG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC 1488
Ser Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
485 490 495

ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC 1536
Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
500 505 510

CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC 1584
His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
515 520 525

AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC 1632
Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro
530 535 540

TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC 1680
Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser
545 550 555 560

CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG 1728
Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
565 570 575

CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC 1776
Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
580 585 590

AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG 1824

Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val
595 600 605

AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC 1872
Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
610 615 620

CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC 1920
Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
625 630 635 640

ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC 1968
Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
645 650 655

CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG 2016
His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
660 665 670

AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC 2064
Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
675 680 685

CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT 2112
Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
690 695 700

CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC 2160
His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
705 710 715 720

ATG GAC GAG CTG TAC AAG TAA 2181
Met Asp Glu Leu Tyr Lys
725

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 726 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly
1 5 10 15
Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp
20 25 30
Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg
35 40 45
Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys
50 55 60
Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp

65 70 75 80
Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg
85 90 95
Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys
100 105 110
Gln Glu Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn
115 120 125
Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg
130 135 140
Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr
145 150 155 160
Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr
165 170 175
Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val
180 185 190
Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro
195 200 205
Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys
210 215 220
Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser
225 230 235 240
Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu
245 250 255
Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr
260 265 270
Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile
275 280 285
Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala
290 295 300
Thr Met Lys Thr Phe Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu Val
305 310 315 320
Leu Glu Asp Asn Asp Tyr Gly Arg Ala Val Asp Trp Trp Gly Leu Gly
325 330 335
Val Val Met Tyr Glu Met Met Cys Gly Arg Leu Pro Phe Tyr Asn Gln
340 345 350
Asp His Glu Lys Leu Phe Glu Leu Ile Leu Met Glu Glu Ile Arg Phe
355 360 365
Pro Arg Thr Leu Gly Pro Glu Ala Lys Ser Leu Leu Ser Gly Leu Leu
370 375 380
Lys Lys Asp Pro Lys Gln Arg Leu Gly Gly Gly Ser Glu Asp Ala Lys
385 390 395 400
Glu Ile Met Gln His Arg Phe Phe Ala Gly Ile Val Trp Gln His Val
405 410 415
Tyr Glu Lys Lys Leu Ser Pro Pro Phe Lys Pro Gln Val Thr Ser Glu
420 425 430
Thr Asp Thr Arg Tyr Phe Asp Glu Glu Phe Thr Ala Gln Met Ile Thr
435 440 445
Ile Thr Pro Pro Asp Gln Asp Asp Ser Met Glu Cys Val Asp Ser Glu
450 455 460
Arg Arg Pro His Phe Pro Gln Phe Ser Tyr Ser Ala Ser Ser Thr Ala
465 470 475 480
Ser Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
485 490 495
Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
500 505 510
His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
515 520 525
Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro

```
    530                 535                 540
Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser
545                 550                 555                 560
Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
                565                 570                 575
Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
            580                 585                 590
Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val
        595                 600                 605
Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
    610                 615                 620
Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
625                 630                 635                 640
Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
                645                 650                 655
His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
            660                 665                 670
Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
        675                 680                 685
Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
    690                 695                 700
His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
705                 710                 715                 720
Met Asp Glu Leu Tyr Lys
                725
```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2751 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2748
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
ATG GCT GAC GTT TAC CCG GCC AAC GAC TCC ACG GCG TCT CAG GAC GTG      48
Met Ala Asp Val Tyr Pro Ala Asn Asp Ser Thr Ala Ser Gln Asp Val
 1               5                  10                  15

GCC AAC CGC TTC GCC CGC AAA GGG GCG CTG AGG CAG AAG AAC GTG CAT      96
Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
            20                  25                  30

GAG GTG AAA GAC CAC AAA TTC ATC GCC CGC TTC TTC AAG CAA CCC ACC     144
Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr
        35                  40                  45

TTC TGC AGC CAC TGC ACC GAC TTC ATC TGG GGG TTT GGG AAA CAA GGC     192
Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly
    50                  55                  60
```

```
TTC CAG TGC CAA GTT TGC TGT TTT GTG GTT CAT AAG AGG TGC CAT GAG      240
Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
65                  70                  75                  80

TTC GTT ACG TTC TCT TGT CCG GGT GCG GAT AAG GGA CCT GAC ACT GAC      288
Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp
                85                  90                  95

GAC CCC AGG AGC AAG CAC AAG TTC AAA ATC CAC ACA TAC GGA AGC CCT      336
Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro
            100                 105                 110

ACC TTC TGT GAT CAC TGT GGG TCC CTG CTC TAT GGA CTT ATC CAC CAA      384
Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
        115                 120                 125

GGG ATG AAA TGT GAC ACC TGC GAC ATG AAT GTT CAC AAC CAG TGT GTG      432
Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val
    130                 135                 140

ATC AAT GAC CCT AGC CTC TGC GGA ATG GAT CAC ACA GAG AAG AGG GGG      480
Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly
145                 150                 155                 160

CGG ATT TAT CTG AAG GCT GAG GTC ACT GAT GAA AAG CTC CAC GTC ACG      528
Arg Ile Tyr Leu Lys Ala Glu Val Thr Asp Glu Lys Leu His Val Thr
                165                 170                 175

GTA CGA GAT GCA AAA AAT CTA ATC CCT ATG GAT CCA AAT GGG CTT TCG      576
Val Arg Asp Ala Lys Asn Leu Ile Pro Met Asp Pro Asn Gly Leu Ser
            180                 185                 190

GAT CCT TAT GTG AAG CTG AAA CTA ATC CCT GAC CCC AAG AAT GAG AGC      624
Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Asn Glu Ser
        195                 200                 205

AAA CAG AAA ACC AAA ACC ATC CGC TCC AAC CTG AAT CCT CAG TGG AAT      672
Lys Gln Lys Thr Lys Thr Ile Arg Ser Asn Leu Asn Pro Gln Trp Asn
    210                 215                 220

GAG TCC TTC ACG TTC AAA TTA AAA CCT TCA GAC AAA GAC CGG CGA CTG      720
Glu Ser Phe Thr Phe Lys Leu Lys Pro Ser Asp Lys Asp Arg Arg Leu
225                 230                 235                 240

TCT GTA GAA ATC TGG GAC TGG GAT CGG ACG ACT CGG AAT GAC TTC ATG      768
Ser Val Glu Ile Trp Asp Trp Asp Arg Thr Thr Arg Asn Asp Phe Met
                245                 250                 255

GGA TCC CTT TCC TTT GGT GTC TCA GAG CTA ATG AAG ATG CCG GCC AGT      816
Gly Ser Leu Ser Phe Gly Val Ser Glu Leu Met Lys Met Pro Ala Ser
            260                 265                 270

GGA TGG TAT AAA GCT CAC AAC CAA GAA GAG GGC GAA TAT TAC AAC GTG      864
Gly Trp Tyr Lys Ala His Asn Gln Glu Glu Gly Glu Tyr Tyr Asn Val
        275                 280                 285

CCC ATT CCA GAA GGA GAT GAA GAA GGC AAC ATG GAA CTC AGG CAG AAG      912
```

```
Pro Ile Pro Glu Gly Asp Glu Glu Gly Asn Met Glu Leu Arg Gln Lys
    290                 295                 300

TTT GAG AAA GCC AAG CTA GGT CCT GTT GGT AAC AAA GTC ATC AGC CCT      960
Phe Glu Lys Ala Lys Leu Gly Pro Val Gly Asn Lys Val Ile Ser Pro
305                 310                 315                 320

TCA GAA GAC AGA AAG CAA CCA TCC AAC AAC CTG GAC AGA GTG AAA CTC     1008
Ser Glu Asp Arg Lys Gln Pro Ser Asn Asn Leu Asp Arg Val Lys Leu
                325                 330                 335

ACA GAC TTC AAC TTC CTC ATG GTG CTG GGG AAG GGG AGT TTT GGG AAG     1056
Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser Phe Gly Lys
            340                 345                 350

GTG ATG CTT GCT GAC AGG AAG GGA ACG GAG GAA CTG TAC GCC ATC AAG     1104
Val Met Leu Ala Asp Arg Lys Gly Thr Glu Glu Leu Tyr Ala Ile Lys
        355                 360                 365

ATC CTG AAG AAG GAC GTG GTG ATC CAG GAC GAC GAC GTG GAG TGC ACC     1152
Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val Glu Cys Thr
    370                 375                 380

ATG GTG GAG AAG CGC GTG CTG GCC CTG CTG GAC AAG CCG CCA TTT CTG     1200
Met Val Glu Lys Arg Val Leu Ala Leu Leu Asp Lys Pro Pro Phe Leu
385                 390                 395                 400

ACA CAG CTG CAC TCC TGC TTC CAG ACA GTG GAC CGG CTG TAC TTC GTC     1248
Thr Gln Leu His Ser Cys Phe Gln Thr Val Asp Arg Leu Tyr Phe Val
                405                 410                 415

ATG GAA TAC GTC AAC GGC GGG GAT CTT ATG TAC CAC ATT CAG CAA GTC     1296
Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln Val
            420                 425                 430

GGG AAA TTT AAG GAG CCA CAA GCA GTA TTC TAC GCA GCC GAG ATC TCC     1344
Gly Lys Phe Lys Glu Pro Gln Ala Val Phe Tyr Ala Ala Glu Ile Ser
        435                 440                 445

ATC GGA CTG TTC TTC CTT CAT AAA AGA GGG ATC ATT TAC AGG GAT CTG     1392
Ile Gly Leu Phe Phe Leu His Lys Arg Gly Ile Ile Tyr Arg Asp Leu
    450                 455                 460

AAG CTG AAC AAT GTC ATG CTG AAC TCA GAA GGG CAC ATC AAA ATC GCC     1440
Lys Leu Asn Asn Val Met Leu Asn Ser Glu Gly His Ile Lys Ile Ala
465                 470                 475                 480

GAC TTC GGG ATG TGC AAG GAA CAC ATG ATG GAT GGA GTC ACG ACC AGG     1488
Asp Phe Gly Met Cys Lys Glu His Met Met Asp Gly Val Thr Thr Arg
                485                 490                 495

ACC TTC TGC GGA ACT CCG GAC TAC ATT GCC CCA GAG ATA ATC GCT TAC     1536
Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Ile Ala Tyr
            500                 505                 510

CAG CCG TAC GGG AAG TCT GTA GAT TGG TGG GCG TAC GGT GTG CTG CTG     1584
Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Tyr Gly Val Leu Leu
        515                 520                 525
```

```
TAC GAG ATG CTA GCC GGG CAG CCT CCG TTT GAT GGT GAA GAT GAA GAT     1632
Tyr Glu Met Leu Ala Gly Gln Pro Pro Phe Asp Gly Glu Asp Glu Asp
    530                 535                 540

GAA CTG TTT CAG TCT ATA ATG GAG CAC AAC GTG TCC TAC CCC AAA TCC     1680
Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ser Tyr Pro Lys Ser
545                 550                 555                 560

TTG TCC AAG GAA GCC GTC TCC ATC TGC AAA GGA CTT ATG ACC AAA CAG     1728
Leu Ser Lys Glu Ala Val Ser Ile Cys Lys Gly Leu Met Thr Lys Gln
                565                 570                 575

CCT GCC AAG CGA CTG GGC TGC GGG CCC GAG GGA GAG AGG GAT GTC AGA     1776
Pro Ala Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg Asp Val Arg
            580                 585                 590

GAG CAT GCC TTC TTC AGG AGG ATC GAC TGG GAG AAA CTG GAG AAC AGG     1824
Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
        595                 600                 605

GAG ATC CAA CCA CCA TTC AAG CCC AAA GTG TGT GGC AAA GGA GCA GAA     1872
Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
    610                 615                 620

AAC TTT GAC AAG TTC TTC ACG CGA GGA CAG CCT GTC TTA ACA CCA CCA     1920
Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
625                 630                 635                 640

GAT CAG CTG GTC ATT GCT AAC ATA GAC CAA TCT GAT TTT GAA GGG TTC     1968
Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                645                 650                 655

TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA     2016
Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
            660                 665                 670

GGG CGC GCC ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA     2064
Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
        675                 680                 685

ATT CTT GTT GAA TTA GAT GGC GAT GTT AAT GGG CAA AAA TTC TCT GTT     2112
Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
    690                 695                 700

AGT GGA GAG GGT GAA GGT GAT GCA ACA TAC GGA AAA CTT ACC CTT AAA     2160
Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
705                 710                 715                 720

TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT GTC     2208
Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
                725                 730                 735

ACT ACT CTC ACT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT     2256
Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
            740                 745                 750

ATG AAA CAG CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA     2304
```

Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
755 760 765

CAG GAA AGA ACT ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT 2352
Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
770 775 780

GCT GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA 2400
Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
785 790 795 800

AAA GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG 2448
Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
805 810 815

GAA TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA 2496
Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
820 825 830

AAG AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT 2544
Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
835 840 845

GGA AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC 2592
Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
850 855 860

GAT GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT 2640
Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
865 870 875 880

GCC CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT 2688
Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
885 890 895

GAG TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC 2736
Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
900 905 910

AAA CCT CAG GAG TAA 2751
Lys Pro Gln Glu
915

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 916 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Met Ala Asp Val Tyr Pro Ala Asn Asp Ser Thr Ala Ser Gln Asp Val

1 5 10 15
Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
20 25 30
Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr
35 40 45
Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly
50 55 60
Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
65 70 75 80
Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp
85 90 95
Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro
100 105 110
Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
115 120 125
Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val
130 135 140
Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly
145 150 155 160
Arg Ile Tyr Leu Lys Ala Glu Val Thr Asp Glu Lys Leu His Val Thr
165 170 175
Val Arg Asp Ala Lys Asn Leu Ile Pro Met Asp Pro Asn Gly Leu Ser
180 185 190
Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Asn Glu Ser
195 200 205
Lys Gln Lys Thr Lys Thr Ile Arg Ser Asn Leu Asn Pro Gln Trp Asn
210 215 220
Glu Ser Phe Thr Phe Lys Leu Lys Pro Ser Asp Lys Asp Arg Arg Leu
225 230 235 240
Ser Val Glu Ile Trp Asp Trp Asp Arg Thr Thr Arg Asn Asp Phe Met
245 250 255
Gly Ser Leu Ser Phe Gly Val Ser Glu Leu Met Lys Met Pro Ala Ser
260 265 270
Gly Trp Tyr Lys Ala His Asn Gln Glu Glu Gly Glu Tyr Tyr Asn Val
275 280 285
Pro Ile Pro Glu Gly Asp Glu Glu Gly Asn Met Glu Leu Arg Gln Lys
290 295 300
Phe Glu Lys Ala Lys Leu Gly Pro Val Gly Asn Lys Val Ile Ser Pro
305 310 315 320
Ser Glu Asp Arg Lys Gln Pro Ser Asn Asn Leu Asp Arg Val Lys Leu
325 330 335
Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser Phe Gly Lys
340 345 350
Val Met Leu Ala Asp Arg Lys Gly Thr Glu Glu Leu Tyr Ala Ile Lys
355 360 365
Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val Glu Cys Thr
370 375 380
Met Val Glu Lys Arg Val Leu Ala Leu Leu Asp Lys Pro Pro Phe Leu
385 390 395 400
Thr Gln Leu His Ser Cys Phe Gln Thr Val Asp Arg Leu Tyr Phe Val
405 410 415
Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln Val
420 425 430
Gly Lys Phe Lys Glu Pro Gln Ala Val Phe Tyr Ala Ala Glu Ile Ser
435 440 445
Ile Gly Leu Phe Phe Leu His Lys Arg Gly Ile Ile Tyr Arg Asp Leu
450 455 460
Lys Leu Asn Asn Val Met Leu Asn Ser Glu Gly His Ile Lys Ile Ala

465 470 475 480
Asp Phe Gly Met Cys Lys Glu His Met Met Asp Gly Val Thr Thr Arg
485 490 495
Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Ile Ala Tyr
500 505 510
Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Tyr Gly Val Leu Leu
515 520 525
Tyr Glu Met Leu Ala Gly Gln Pro Pro Phe Asp Gly Glu Asp Glu Asp
530 535 540
Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ser Tyr Pro Lys Ser
545 550 555 560
Leu Ser Lys Glu Ala Val Ser Ile Cys Lys Gly Leu Met Thr Lys Gln
565 570 575
Pro Ala Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg Asp Val Arg
580 585 590
Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
595 600 605
Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
610 615 620
Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
625 630 635 640
Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
645 650 655
Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
660 665 670
Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
675 680 685
Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
690 695 700
Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
705 710 715 720
Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
725 730 735
Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
740 745 750
Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
755 760 765
Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
770 775 780
Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
785 790 795 800
Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
805 810 815
Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
820 825 830
Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
835 840 845
Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
850 855 860
Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
865 870 875 880
Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
885 890 895
Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
900 905 910
Lys Pro Gln Glu
915

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2157 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2154
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
ATG TCG TCC ATC TTG CCA TTC ACG CCG CCA GTT GTG AAG AGA CTG CTG      48
Met Ser Ser Ile Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu
 1               5                  10                  15

GGA TGG AAG AAG TCA GCT GGT GGG TCT GGA GGA GCA GGC GGA GGA GAG      96
Gly Trp Lys Lys Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu
            20                  25                  30

CAG AAT GGG CAG GAA GAA AAG TGG TGT GAG AAA GCA GTG AAA AGT CTG     144
Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu
        35                  40                  45

GTG AAG AAG CTA AAG AAA ACA GGA CGA TTA GAT GAG CTT GAG AAA GCC     192
Val Lys Lys Leu Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala
    50                  55                  60

ATC ACC ACT CAA AAC TGT AAT ACT AAA TGT GTT ACC ATA CCA AGC ACT     240
Ile Thr Thr Gln Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr
65                  70                  75                  80

TGC TCT GAA ATT TGG GGA CTG AGT ACA CCA AAT ACG ATA GAT CAG TGG     288
Cys Ser Glu Ile Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp
                85                  90                  95

GAT ACA ACA GGC CTT TAC AGC TTC TCT GAA CAA ACC AGG TCT CTT GAT     336
Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp
            100                 105                 110

GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT     384
Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr
        115                 120                 125

TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG     432
Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys
    130                 135                 140

GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA     480
Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val
145                 150                 155                 160

TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT     528
```

Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro
165 170 175

CCA GTA TTA GTG CCC CGA CAC ACC GAG ATC CTA ACA GAA CTT CCG CCT 576
Pro Val Leu Val Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro
180 185 190

CTG GAT GAC TAT ACT CAC TCC ATT CCA GAA AAC ACT AAC TTC CCA GCA 624
Leu Asp Asp Tyr Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala
195 200 205

GGA ATT GAG CCA CAG AGT AAT TAT ATT CCA GAA ACG CCA CCT CCT GGA 672
Gly Ile Glu Pro Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly
210 215 220

TAT ATC AGT GAA GAT GGA GAA ACA AGT GAC CAA CAG TTG AAT CAA AGT 720
Tyr Ile Ser Glu Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser
225 230 235 240

ATG GAC ACA GGC TCT CCA GCA GAA CTA TCT CCT ACT ACT CTT TCC CCT 768
Met Asp Thr Gly Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro
245 250 255

GTT AAT CAT AGC TTG GAT TTA CAG CCA GTT ACT TAC TCA GAA CCT GCA 816
Val Asn His Ser Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala
260 265 270

TTT TGG TGT TCA ATA GCA TAT TAT GAA TTA AAT CAG AGG GTT GGA GAA 864
Phe Trp Cys Ser Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu
275 280 285

ACC TTC CAT GCA TCA CAG CCC TCA CTC ACT GTA GAT GGC TTT ACA GAC 912
Thr Phe His Ala Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp
290 295 300

CCA TCA AAT TCA GAG AGG TTC TGC TTA GGT TTA CTC TCC AAT GTT AAC 960
Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn
305 310 315 320

CGA AAT GCC ACG GTA GAA ATG ACA AGA AGG CAT ATA GGA AGA GGA GTG 1008
Arg Asn Ala Thr Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val
325 330 335

CGC TTA TAC TAC ATA GGT GGG GAA GTT TTT GCT GAG TGC CTA AGT GAT 1056
Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp
340 345 350

AGT GCA ATC TTT GTG CAG AGC CCC AAT TGT AAT CAG AGA TAT GGC TGG 1104
Ser Ala Ile Phe Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp
355 360 365

CAC CCT GCA ACA GTG TGT AAA ATT CCA CCA GGC TGT AAT CTG AAG ATC 1152
His Pro Ala Thr Val Cys Lys Ile Pro Pro Gly Cys Asn Leu Lys Ile
370 375 380

TTC AAC AAC CAG GAA TTT GCT GCT CTT CTG GCT CAG TCT GTT AAT CAG 1200
Phe Asn Asn Gln Glu Phe Ala Ala Leu Leu Ala Gln Ser Val Asn Gln
385 390 395 400

```
GGT TTT GAA GCC GTC TAT CAG CTA ACT AGA ATG TGC ACC ATA AGA ATG     1248
Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met
                405                 410                 415

AGT TTT GTG AAA GGG TGG GGA GCA GAA TAC CGA AGG CAG ACG GTA ACA     1296
Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr
            420                 425                 430

AGT ACT CCT TGC TGG ATT GAA CTT CAT CTG AAT GGA CCT CTA CAG TGG     1344
Ser Thr Pro Cys Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp
        435                 440                 445

TTG GAC AAA GTA TTA ACT CAG ATG GGA TCC CCT TCA GTG CGT TGC TCA     1392
Leu Asp Lys Val Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser
    450                 455                 460

AGC ATG TCA TGG GTA CCG CGG GCC CGG GAT CCA CCG GTC GCC ACC ATG     1440
Ser Met Ser Trp Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met
465                 470                 475                 480

GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC     1488
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
                485                 490                 495

GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG     1536
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
            500                 505                 510

GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC     1584
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
        515                 520                 525

ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG     1632
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
    530                 535                 540

ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG     1680
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
545                 550                 555                 560

CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC     1728
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
                565                 570                 575

ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG     1776
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
            580                 585                 590

AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC     1824
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
        595                 600                 605

GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC     1872
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
    610                 615                 620

TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC     1920
```

```
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
625                 630                 635                 640

ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG     1968
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
                645                 650                 655

CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC     2016
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
            660                 665                 670

GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC     2064
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
        675                 680                 685

AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG     2112
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
    690                 695                 700

ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA         2157
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
705                 710                 715
```

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 718 amino acids
  (B) TYPE: amino acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
Met Ser Ser Ile Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu
 1               5                  10                  15
Gly Trp Lys Lys Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu
            20                  25                  30
Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu
        35                  40                  45
Val Lys Lys Leu Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala
    50                  55                  60
Ile Thr Thr Gln Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr
65                  70                  75                  80
Cys Ser Glu Ile Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp
                85                  90                  95
Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp
            100                 105                 110
Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr
        115                 120                 125
Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys
    130                 135                 140
Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val
145                 150                 155                 160
Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro
```

```
                165                 170                 175
Pro Val Leu Val Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro
            180                 185                 190
Leu Asp Asp Tyr Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala
        195                 200                 205
Gly Ile Glu Pro Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly
    210                 215                 220
Tyr Ile Ser Glu Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser
225                 230                 235                 240
Met Asp Thr Gly Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro
                245                 250                 255
Val Asn His Ser Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala
            260                 265                 270
Phe Trp Cys Ser Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu
        275                 280                 285
Thr Phe His Ala Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp
    290                 295                 300
Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn
305                 310                 315                 320
Arg Asn Ala Thr Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val
                325                 330                 335
Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp
            340                 345                 350
Ser Ala Ile Phe Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp
        355                 360                 365
His Pro Ala Thr Val Cys Lys Ile Pro Pro Gly Cys Asn Leu Lys Ile
    370                 375                 380
Phe Asn Asn Gln Glu Phe Ala Ala Leu Leu Ala Gln Ser Val Asn Gln
385                 390                 395                 400
Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met
                405                 410                 415
Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr
            420                 425                 430
Ser Thr Pro Cys Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp
        435                 440                 445
Leu Asp Lys Val Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser
    450                 455                 460
Ser Met Ser Trp Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met
465                 470                 475                 480
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
                485                 490                 495
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
            500                 505                 510
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
        515                 520                 525
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
    530                 535                 540
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
545                 550                 555                 560
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
                565                 570                 575
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
            580                 585                 590
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
        595                 600                 605
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
    610                 615                 620
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
```

```
625                 630                 635                 640
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
                645                 650                 655
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
            660                 665                 670
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
        675                 680                 685
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
    690                 695                 700
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
705                 710                 715
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2397 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2394
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
ATG GAC AAT ATG TCT ATT ACG AAT ACA CCA ACA AGT AAT GAT GCC TGT      48
Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys
 1               5                  10                  15

CTG AGC ATT GTG CAT AGT TTG ATG TGC CAT AGA CAA GGT GGA GAG AGT      96
Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser
            20                  25                  30

GAA ACA TTT GCA AAA AGA GCA ATT GAA AGT TTG GTA AAG AAG CTG AAG     144
Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys
        35                  40                  45

GAG AAA AAA GAT GAA TTG GAT TCT TTA ATA ACA GCT ATA ACT ACA AAT     192
Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn
    50                  55                  60

GGA GCT CAT CCT AGT AAA TGT GTT ACC ATA CAG AGA ACA TTG GAT GGG     240
Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly
65                  70                  75                  80

AGG CTT CAG GTG GCT GGT CGG AAA GGA TTT CCT CAT GTG ATC TAT GCC     288
Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala
                85                  90                  95

CGT CTC TGG AGG TGG CCT GAT CTT CAC AAA AAT GAA CTA AAA CAT GTT     336
Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val
            100                 105                 110

AAA TAT TGT CAG TAT GCG TTT GAC TTA AAA TGT GAT AGT GTC TGT GTG     384
```

Lys Tyr Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val
115 120 125

AAT CCA TAT CAC TAC GAA CGA GTT GTA TCA CCT GGA ATT GAT CTC TCA 432
Asn Pro Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser
130 135 140

GGA TTA ACA CTG CAG AGT AAT GCT CCA TCA AGT ATG ATG GTG AAG GAT 480
Gly Leu Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp
145 150 155 160

GAA TAT GTG CAT GAC TTT GAG GGA CAG CCA TCG TTG TCC ACT GAA GGA 528
Glu Tyr Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly
165 170 175

CAT TCA ATT CAA ACC ATC CAG CAT CCA CCA AGT AAT CGT GCA TCG ACA 576
His Ser Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr
180 185 190

GAG ACA TAC AGC ACC CCA GCT CTG TTA GCC CCA TCT GAG TCT AAT GCT 624
Glu Thr Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala
195 200 205

ACC AGC ACT GCC AAC TTT CCC AAC ATT CCT GTG GCT TCC ACA AGT CAG 672
Thr Ser Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln
210 215 220

CCT GCC AGT ATA CTG GGG GGC AGC CAT AGT GAA GGA CTG TTG CAG ATA 720
Pro Ala Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile
225 230 235 240

GCA TCA GGG CCT CAG CCA GGA CAG CAG CAG AAT GGA TTT ACT GGT CAG 768
Ala Ser Gly Pro Gln Pro Gly Gln Gln Gln Asn Gly Phe Thr Gly Gln
245 250 255

CCA GCT ACT TAC CAT CAT AAC AGC ACT ACC ACC TGG ACT GGA AGT AGG 816
Pro Ala Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg
260 265 270

ACT GCA CCA TAC ACA CCT AAT TTG CCT CAC CAC CAA AAC GGC CAT CTT 864
Thr Ala Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu
275 280 285

CAG CAC CAC CCG CCT ATG CCG CCC CAT CCC GGA CAT TAC TGG CCT GTT 912
Gln His His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val
290 295 300

CAC AAT GAG CTT GCA TTC CAG CCT CCC ATT TCC AAT CAT CCT GCT CCT 960
His Asn Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro
305 310 315 320

GAG TAT TGG TGT TCC ATT GCT TAC TTT GAA ATG GAT GTT CAG GTA GGA 1008
Glu Tyr Trp Cys Ser Ile Ala Tyr Phe Glu Met Asp Val Gln Val Gly
325 330 335

GAG ACA TTT AAG GTT CCT TCA AGC TGC CCT ATT GTT ACT GTT GAT GGA 1056
Glu Thr Phe Lys Val Pro Ser Ser Cys Pro Ile Val Thr Val Asp Gly
340 345 350

TAC GTG GAC CCT TCT GGA GGA GAT CGC TTT TGT TTG GGT CAA CTC TCC 1104
Tyr Val Asp Pro Ser Gly Gly Asp Arg Phe Cys Leu Gly Gln Leu Ser
355 360 365

AAT GTC CAC AGG ACA GAA GCC ATT GAG AGA GCA AGG TTG CAC ATA GGC 1152
Asn Val His Arg Thr Glu Ala Ile Glu Arg Ala Arg Leu His Ile Gly
370 375 380

AAA GGT GTG CAG TTG GAA TGT AAA GGT GAA GGT GAT GTT TGG GTC AGG 1200
Lys Gly Val Gln Leu Glu Cys Lys Gly Glu Gly Asp Val Trp Val Arg
385 390 395 400

TGC CTT AGT GAC CAC GCG GTC TTT GTA CAG AGT TAC TAC TTA GAC AGA 1248
Cys Leu Ser Asp His Ala Val Phe Val Gln Ser Tyr Tyr Leu Asp Arg
405 410 415

GAA GCT GGG CGT GCA CCT GGA GAT GCT GTT CAT AAG ATC TAC CCA AGT 1296
Glu Ala Gly Arg Ala Pro Gly Asp Ala Val His Lys Ile Tyr Pro Ser
420 425 430

GCA TAT ATA AAG GTC TTT GAT TTG CGT CAG TGT CAT CGA CAG ATG CAG 1344
Ala Tyr Ile Lys Val Phe Asp Leu Arg Gln Cys His Arg Gln Met Gln
435 440 445

CAG CAG GCG GCT ACT GCA CAA GCT GCA GCA GCT GCC CAG GCA GCA GCC 1392
Gln Gln Ala Ala Thr Ala Gln Ala Ala Ala Ala Ala Gln Ala Ala Ala
450 455 460

GTG GCA GGA AAC ATC CCT GGC CCA GGA TCA GTA GGT GGA ATA GCT CCA 1440
Val Ala Gly Asn Ile Pro Gly Pro Gly Ser Val Gly Gly Ile Ala Pro
465 470 475 480

GCT ATC AGT CTG TCA GCT GCT GCT GGA ATT GGT GTT GAT GAC CTT CGT 1488
Ala Ile Ser Leu Ser Ala Ala Ala Gly Ile Gly Val Asp Asp Leu Arg
485 490 495

CGC TTA TGC ATA CTC AGG ATG AGT TTT GTG AAA GGC TGG GGA CCG GAT 1536
Arg Leu Cys Ile Leu Arg Met Ser Phe Val Lys Gly Trp Gly Pro Asp
500 505 510

TAC CCA AGA CAG AGC ATC AAA GAA ACA CCT TGC TGG ATT GAA ATT CAC 1584
Tyr Pro Arg Gln Ser Ile Lys Glu Thr Pro Cys Trp Ile Glu Ile His
515 520 525

TTA CAC CGG GCC CTC CAG CTC CTA GAC GAA GTA CTT CAT ACC ATG CCG 1632
Leu His Arg Ala Leu Gln Leu Leu Asp Glu Val Leu His Thr Met Pro
530 535 540

ATT GCA GAC CCA CAA CCT TTA GAC TGG GAT CCA CCG GTC GCC ACC ATG 1680
Ile Ala Asp Pro Gln Pro Leu Asp Trp Asp Pro Pro Val Ala Thr Met
545 550 555 560

GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC 1728
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
565 570 575

GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG 1776

```
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
            580                 585                 590

GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC     1824
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
        595                 600                 605

ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG     1872
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
    610                 615                 620

ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG     1920
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
625                 630                 635                 640

CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC     1968
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
                645                 650                 655

ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG     2016
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
            660                 665                 670

AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC     2064
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
        675                 680                 685

GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC     2112
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
    690                 695                 700

TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC     2160
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
705                 710                 715                 720

ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG     2208
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
                725                 730                 735

CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC     2256
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
            740                 745                 750

GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC     2304
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
        755                 760                 765

AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG     2352
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
    770                 775                 780

ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA         2397
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785                 790                 795
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 798 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys
 1               5                  10                  15
Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser
            20                  25                  30
Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys
        35                  40                  45
Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn
    50                  55                  60
Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly
65                  70                  75                  80
Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala
                85                  90                  95
Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val
            100                 105                 110
Lys Tyr Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val
        115                 120                 125
Asn Pro Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser
    130                 135                 140
Gly Leu Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp
145                 150                 155                 160
Glu Tyr Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly
                165                 170                 175
His Ser Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr
            180                 185                 190
Glu Thr Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala
        195                 200                 205
Thr Ser Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln
    210                 215                 220
Pro Ala Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile
225                 230                 235                 240
Ala Ser Gly Pro Gln Pro Gly Gln Gln Gln Asn Gly Phe Thr Gly Gln
                245                 250                 255
Pro Ala Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg
            260                 265                 270
Thr Ala Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu
        275                 280                 285
Gln His His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val
    290                 295                 300
His Asn Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro
305                 310                 315                 320
Glu Tyr Trp Cys Ser Ile Ala Tyr Phe Glu Met Asp Val Gln Val Gly
                325                 330                 335
Glu Thr Phe Lys Val Pro Ser Ser Cys Pro Ile Val Thr Val Asp Gly
            340                 345                 350
Tyr Val Asp Pro Ser Gly Gly Asp Arg Phe Cys Leu Gly Gln Leu Ser
        355                 360                 365
Asn Val His Arg Thr Glu Ala Ile Glu Arg Ala Arg Leu His Ile Gly
```

```
    370                 375                 380
Lys Gly Val Gln Leu Glu Cys Lys Gly Glu Gly Asp Val Trp Val Arg
385                 390                 395                 400
Cys Leu Ser Asp His Ala Val Phe Val Gln Ser Tyr Tyr Leu Asp Arg
                405                 410                 415
Glu Ala Gly Arg Ala Pro Gly Asp Ala Val His Lys Ile Tyr Pro Ser
            420                 425                 430
Ala Tyr Ile Lys Val Phe Asp Leu Arg Gln Cys His Arg Gln Met Gln
        435                 440                 445
Gln Gln Ala Ala Thr Ala Gln Ala Ala Ala Ala Ala Gln Ala Ala Ala
    450                 455                 460
Val Ala Gly Asn Ile Pro Gly Pro Gly Ser Val Gly Gly Ile Ala Pro
465                 470                 475                 480
Ala Ile Ser Leu Ser Ala Ala Ala Gly Ile Gly Val Asp Asp Leu Arg
                485                 490                 495
Arg Leu Cys Ile Leu Arg Met Ser Phe Val Lys Gly Trp Gly Pro Asp
            500                 505                 510
Tyr Pro Arg Gln Ser Ile Lys Glu Thr Pro Cys Trp Ile Glu Ile His
        515                 520                 525
Leu His Arg Ala Leu Gln Leu Leu Asp Glu Val Leu His Thr Met Pro
    530                 535                 540
Ile Ala Asp Pro Gln Pro Leu Asp Trp Asp Pro Pro Val Ala Thr Met
545                 550                 555                 560
Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
                565                 570                 575
Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
            580                 585                 590
Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
        595                 600                 605
Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
    610                 615                 620
Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
625                 630                 635                 640
His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
                645                 650                 655
Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
            660                 665                 670
Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
        675                 680                 685
Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
    690                 695                 700
Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
705                 710                 715                 720
Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
                725                 730                 735
Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
            740                 745                 750
Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
        755                 760                 765
Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
    770                 775                 780
Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785                 790                 795
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3138 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3135
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

ATG GCG GGC TGG ATC CAG GCC CAG CAG CTG CAG GGA GAC GCG CTG CGC 48
Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg
1 5 10 15

CAG ATG CAG GTG CTG TAC GGC CAG CAC TTC CCC ATC GAG GTC CGG CAC 96
Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His
20 25 30

TAC TTG GCC CAG TGG ATT GAG AGC CAG CCA TGG GAT GCC ATT GAC TTG 144
Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu
35 40 45

GAC AAT CCC CAG GAC AGA GCC CAA GCC ACC CAG CTC CTG GAG GGC CTG 192
Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu
50 55 60

GTG CAG GAG CTG CAG AAG AAG GCG GAG CAC CAG GTG GGG GAA GAT GGG 240
Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly
65 70 75 80

TTT TTA CTG AAG ATC AAG CTG GGG CAC TAC GCC ACG CAG CTC CAG AAA 288
Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys
85 90 95

ACA TAT GAC CGC TGC CCC CTG GAG CTG GTC CGC TGC ATC CGG CAC ATT 336
Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile
100 105 110

CTG TAC AAT GAA CAG AGG CTG GTC CGA GAA GCC AAC AAT TGC AGC TCT 384
Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser
115 120 125

CCG GCT GGG ATC CTG GTT GAC GCC ATG TCC CAG AAG CAC CTT CAG ATC 432
Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile
130 135 140

AAC CAG ACA TTT GAG GAG CTG CGA CTG GTC ACG CAG GAC ACA GAG AAT 480
Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn
145 150 155 160

GAG CTG AAG AAA CTG CAG CAG ACT CAG GAG TAC TTC ATC ATC CAG TAC 528
Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr
165 170 175

CAG GAG AGC CTG AGG ATC CAA GCT CAG TTT GCC CAG CTG GCC CAG CTG 576

Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu
180 185 190

AGC CCC CAG GAG CGT CTG AGC CGG GAG ACG GCC CTC CAG CAG AAG CAG 624
Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln
195 200 205

GTG TCT CTG GAG GCC TGG TTG CAG CGT GAG GCA CAG ACA CTG CAG CAG 672
Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln
210 215 220

TAC CGC GTG GAG CTG GCC GAG AAG CAC CAG AAG ACC CTG CAG CTG CTG 720
Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu
225 230 235 240

CGG AAG CAG CAG ACC ATC ATC CTG GAT GAC GAG CTG ATC CAG TGG AAG 768
Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys
245 250 255

CGG CGG CAG CAG CTG GCC GGG AAC GGC GGG CCC CCC GAG GGC AGC CTG 816
Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu
260 265 270

GAC GTG CTA CAG TCC TGG TGT GAG AAG TTG GCC GAG ATC ATC TGG CAG 864
Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln
275 280 285

AAC CGG CAG CAG ATC CGC AGG GCT GAG CAC CTC TGC CAG CAG CTG CCC 912
Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu Cys Gln Gln Leu Pro
290 295 300

ATC CCC GGC CCA GTG GAG GAG ATG CTG GCC GAG GTC AAC GCC ACC ATC 960
Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu Val Asn Ala Thr Ile
305 310 315 320

ACG GAC ATT ATC TCA GCC CTG GTG ACC AGC ACA TTC ATC ATT GAG AAG 1008
Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr Phe Ile Ile Glu Lys
325 330 335

CAG CCT CCT CAG GTC CTG AAG ACC CAG ACC AAG TTT GCA GCC ACC GTA 1056
Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys Phe Ala Ala Thr Val
340 345 350

CGC CTG CTG GTG GGC GGG AAG CTG AAC GTG CAC ATG AAT CCC CCC CAG 1104
Arg Leu Leu Val Gly Gly Lys Leu Asn Val His Met Asn Pro Pro Gln
355 360 365

GTG AAG GCC ACC ATC ATC AGT GAG CAG CAG GCC AAG TCT CTG CTT AAA 1152
Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala Lys Ser Leu Leu Lys
370 375 380

AAT GAG AAC ACC CGC AAC GAG TGC AGT GGT GAG ATC CTG AAC AAC TGC 1200
Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys
385 390 395 400

TGC GTG ATG GAG TAC CAC CAA GCC ACG GGC ACC CTC AGT GCC CAC TTC 1248
Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr Leu Ser Ala His Phe
405 410 415

AGG AAC ATG TCA CTG AAG AGG ATC AAG CGT GCT GAC CGG CGG GGT GCA 1296
Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala Asp Arg Arg Gly Ala
420 425 430

GAG TCC GTG ACA GAG GAG AAG TTC ACA GTC CTG TTT GAG TCT CAG TTC 1344
Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu Phe Glu Ser Gln Phe
435 440 445

AGT GTT GGC AGC AAT GAG CTT GTG TTC CAG GTG AAG ACT CTG TCC CTA 1392
Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val Lys Thr Leu Ser Leu
450 455 460

CCT GTG GTT GTC ATC GTC CAC GGC AGC CAG GAC CAC AAT GCC ACG GCT 1440
Pro Val Val Val Ile Val His Gly Ser Gln Asp His Asn Ala Thr Ala
465 470 475 480

ACT GTG CTG TGG GAC AAT GCC TTT GCT GAG CCG GGC AGG GTG CCA TTT 1488
Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro Gly Arg Val Pro Phe
485 490 495

GCC GTG CCT GAC AAA GTG CTG TGG CCG CAG CTG TGT GAG GCG CTC AAC 1536
Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu Cys Glu Ala Leu Asn
500 505 510

ATG AAA TTC AAG GCC GAA GTG CAG AGC AAC CGG GGC CTG ACC AAG GAG 1584
Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg Gly Leu Thr Lys Glu
515 520 525

AAC CTC GTG TTC CTG GCG CAG AAA CTG TTC AAC AAC AGC AGC AGC CAC 1632
Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Ser Ser Ser His
530 535 540

CTG GAG GAC TAC AGT GGC CTG TCC GTG TCC TGG TCC CAG TTC AAC AGG 1680
Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp Ser Gln Phe Asn Arg
545 550 555 560

GAG AAC TTG CCG GGC TGG AAC TAC ACC TTC TGG CAG TGG TTT GAC GGG 1728
Glu Asn Leu Pro Gly Trp Asn Tyr Thr Phe Trp Gln Trp Phe Asp Gly
565 570 575

GTG ATG GAG GTG TTG AAG AAG CAC CAC AAG CCC CAC TGG AAT GAT GGG 1776
Val Met Glu Val Leu Lys Lys His His Lys Pro His Trp Asn Asp Gly
580 585 590

GCC ATC CTA GGT TTT GTG AAT AAG CAA CAG GCC CAC GAC CTG CTC ATC 1824
Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala His Asp Leu Leu Ile
595 600 605

AAC AAG CCC GAC GGG ACC TTC TTG TTG CGC TTT AGT GAC TCA GAA ATC 1872
Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe Ser Asp Ser Glu Ile
610 615 620

GGG GGC ATC ACC ATC GCC TGG AAG TTT GAC TCC CCG GAA CGC AAC CTG 1920
Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser Pro Glu Arg Asn Leu
625 630 635 640

TGG AAC CTG AAA CCA TTC ACC ACG CGG GAT TTC TCC ATC AGG TCC CTG 1968

```
Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe Ser Ile Arg Ser Leu
                645                 650                 655

GCT GAC CGG CTG GGG GAC CTG AGC TAT CTC ATC TAT GTG TTT CCT GAC      2016
Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile Tyr Val Phe Pro Asp
            660                 665                 670

CGC CCC AAG GAT GAG GTC TTC TCC AAG TAC TAC ACT CCT GTG CTG GCT      2064
Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr Thr Pro Val Leu Ala
        675                 680                 685

AAA GCT GTT GAT GGA TAT GTG AAA CCA CAG ATC AAG CAA GTG GTC CCT      2112
Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile Lys Gln Val Val Pro
    690                 695                 700

GAG TTT GTG AAT GCA TCT GCA GAT GCT GGG GGC AGC AGC GCC ACG TAC      2160
Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr
705                 710                 715                 720

ATG GAC CAG GCC CCC TCC CCA GCT GTG TGC CCC CAG GCT CCC TAT AAC      2208
Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro Gln Ala Pro Tyr Asn
                725                 730                 735

ATG TAC CCA CAG AAC CCT GAC CAT GTA CTC GAT CAG GAT GGA GAA TTC      2256
Met Tyr Pro Gln Asn Pro Asp His Val Leu Asp Gln Asp Gly Glu Phe
            740                 745                 750

GAC CTG GAT GAG ACC ATG GAT GTG GCC AGG CAC GTG GAG GAA CTC TTA      2304
Asp Leu Asp Glu Thr Met Asp Val Ala Arg His Val Glu Glu Leu Leu
        755                 760                 765

CGC CGA CCA ATG GAC AGT CTT GAC TCC CGC CTC TCG CCC CCT GCC GGT      2352
Arg Arg Pro Met Asp Ser Leu Asp Ser Arg Leu Ser Pro Pro Ala Gly
    770                 775                 780

CTT TTC ACC TCT GCC AGA GGC TCC CTC TCA TGG GTA CCG CGG GCC CGG      2400
Leu Phe Thr Ser Ala Arg Gly Ser Leu Ser Trp Val Pro Arg Ala Arg
785                 790                 795                 800

GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC      2448
Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr
                805                 810                 815

GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC      2496
Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His
            820                 825                 830

AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG      2544
Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys
        835                 840                 845

CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG      2592
Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp
    850                 855                 860

CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC      2640
Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg
865                 870                 875                 880
```

TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC 2688
Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro
885 890 895

GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC 2736
Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn
900 905 910

TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC 2784
Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn
915 920 925

CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG 2832
Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu
930 935 940

GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG 2880
Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met
945 950 955 960

GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC 2928
Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His
965 970 975

AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC 2976
Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn
980 985 990

ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG 3024
Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu
995 1000 1005

AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC 3072
Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His
1010 1015 1020

ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG 3120
Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met
1025 1030 1035 1040

GAC GAG CTG TAC AAG TAA 3138
Asp Glu Leu Tyr Lys
1045

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1045 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg
1 5 10 15
Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His
20 25 30
Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu
35 40 45
Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu
50 55 60
Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly
65 70 75 80
Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys
85 90 95
Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile
100 105 110
Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser
115 120 125
Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile
130 135 140
Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn
145 150 155 160
Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr
165 170 175
Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu
180 185 190
Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln
195 200 205
Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln
210 215 220
Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu
225 230 235 240
Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys
245 250 255
Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu
260 265 270
Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln
275 280 285
Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu Cys Gln Gln Leu Pro
290 295 300
Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu Val Asn Ala Thr Ile
305 310 315 320
Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr Phe Ile Ile Glu Lys
325 330 335
Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys Phe Ala Ala Thr Val
340 345 350
Arg Leu Leu Val Gly Gly Lys Leu Asn Val His Met Asn Pro Pro Gln
355 360 365
Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala Lys Ser Leu Leu Lys
370 375 380
Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys
385 390 395 400
Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr Leu Ser Ala His Phe
405 410 415
Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala Asp Arg Arg Gly Ala
420 425 430
Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu Phe Glu Ser Gln Phe
435 440 445
Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val Lys Thr Leu Ser Leu

450 455 460
Pro Val Val Val Ile Val His Gly Ser Gln Asp His Asn Ala Thr Ala
465 470 475 480
Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro Gly Arg Val Pro Phe
485 490 495
Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu Cys Glu Ala Leu Asn
500 505 510
Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg Gly Leu Thr Lys Glu
515 520 525
Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Ser Ser Ser His
530 535 540
Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp Ser Gln Phe Asn Arg
545 550 555 560
Glu Asn Leu Pro Gly Trp Asn Tyr Thr Phe Trp Gln Trp Phe Asp Gly
565 570 575
Val Met Glu Val Leu Lys Lys His His Lys Pro His Trp Asn Asp Gly
580 585 590
Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala His Asp Leu Leu Ile
595 600 605
Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe Ser Asp Ser Glu Ile
610 615 620
Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser Pro Glu Arg Asn Leu
625 630 635 640
Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe Ser Ile Arg Ser Leu
645 650 655
Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile Tyr Val Phe Pro Asp
660 665 670
Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr Thr Pro Val Leu Ala
675 680 685
Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile Lys Gln Val Val Pro
690 695 700
Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr
705 710 715 720
Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro Gln Ala Pro Tyr Asn
725 730 735
Met Tyr Pro Gln Asn Pro Asp His Val Leu Asp Gln Asp Gly Glu Phe
740 745 750
Asp Leu Asp Glu Thr Met Asp Val Ala Arg His Val Glu Glu Leu Leu
755 760 765
Arg Arg Pro Met Asp Ser Leu Asp Ser Arg Leu Ser Pro Pro Ala Gly
770 775 780
Leu Phe Thr Ser Ala Arg Gly Ser Leu Ser Trp Val Pro Arg Ala Arg
785 790 795 800
Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr
805 810 815
Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His
820 825 830
Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys
835 840 845
Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp
850 855 860
Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg
865 870 875 880
Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro
885 890 895
Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn
900 905 910
Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn

```
    915                 920                 925
Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu
    930                 935                 940
Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met
945                 950                 955                 960
Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His
                965                 970                 975
Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn
            980                 985                 990
Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu
        995                1000                1005
Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His
   1010                1015                1020
Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met
025                1030                1035                1040
Asp Glu Leu Tyr Lys
               1045
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TGGGATCCTC AGGCCGTGCT GCTGGCCG 28

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GTCTCGAGGG AGCATGGGCA CCTTGCG 27

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

TGGGATCCGA GAAGTCTATA TCCCATC 27

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

TGGGATCCTT AGAAGTCTAT ATCCCATC 28

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

GTCTCGAGCC ATGAACGCCC CCGAGCGG 28

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

GTGAATTCTC GTCTGATTTC TGGCAGGAGG 30

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

GTGAATTCTT TACGTCTGAT TTCTGGCAGG 30

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC 34

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GTGGATCCAA GGAGCTGATC TGACTCAGCA G 31

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG 32

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

CCTCCTAAGC TTATCATGGA CCATTATGAT TC 32

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG 33

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG 45

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTTC TTCCC 45

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

GGGAAGCTTC CATGAGCGAG ACGGTCATC 29

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

CCCGGATCCT CAGGGAGAAC CCCGCTTC 28

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

GTGAATTCGA CCATGGAGCG GCCCCCGGGG 30

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

GTGGTACCCA TTCTGTTAAC CAACTCC 27

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GTGGTACCTC ATTCTGTTAA CCAACTCC 28

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

GTCTCGAGAG ATGCTGTCCC GTGGGTGG 28

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

GTGAATTCGC TTCCTCTTGA GGGAACC 27

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

GTGAATTCAC TTCCTCTTGA GGGAACC 27

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

GTCTCGAGCC ATGGAGAACT TCCAAAAGG 29

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GTGGATCCCA GAGTCGAAGA TGGGGTAC 28

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

GTGGATCCTC AGAGTCGAAG ATGGGGTAC 29

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

GTGAATTCGG CGATGCCAGA CCCCGCGGCG 30

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC 32

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

GTGGATCCTC AGGCACAGGC AGCCTCAGCC TTC 33

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2616 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2613
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG      48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC      96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
```

```
GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC      144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC      192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG      240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG      288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG      336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC      384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC      432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC      480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC      528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC      576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG      624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC      672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC      720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG GCG ATG CCA GAC CCC      768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Ala Met Pro Asp Pro
                245                 250                 255

GCG GCG CAC CTG CCC TTC TTC TAC GGC AGC ATC TCG CGT GCC GAG GCC      816
```

```
Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala
            260                 265                 270

GAG GAG CAC CTG AAG CTG GCG GGC ATG GCG GAC GGG CTC TTC CTG CTG      864
Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly Leu Phe Leu Leu
        275                 280                 285

CGC CAG TGC CTG CGC TCG CTG GGC GGC TAT GTG CTG TCG CTC GTG CAC      912
Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His
    290                 295                 300

GAT GTG CGC TTC CAC CAC TTT CCC ATC GAG CGC CAG CTC AAC GGC ACC      960
Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln Leu Asn Gly Thr
305                 310                 315                 320

TAC GCC ATT GCC GGC GGC AAA GCG CAC TGT GGA CCG GCA GAG CTC TGC     1008
Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro Ala Glu Leu Cys
                325                 330                 335

GAG TTC TAC TCG CGC GAC CCC GAC GGG CTG CCC TGC AAC CTG CGC AAG     1056
Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys
            340                 345                 350

CCG TGC AAC CGG CCG TCG GGC CTC GAG CCG CAG CCG GGG GTC TTC GAC     1104
Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro Gly Val Phe Asp
        355                 360                 365

TGC CTG CGA GAC GCC ATG GTG CGT GAC TAC GTG CGC CAG ACG TGG AAG     1152
Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg Gln Thr Trp Lys
    370                 375                 380

CTG GAG GGC GAG GCC CTG GAG CAG GCC ATC ATC AGC CAG GCC CCG CAG     1200
Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln
385                 390                 395                 400

GTG GAG AAG CTC ATT GCT ACG ACG GCC CAC GAG CGG ATG CCC TGG TAC     1248
Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr
                405                 410                 415

CAC AGC AGC CTG ACG CGT GAG GAG GCC GAG CGC AAA CTT TAC TCT GGG     1296
His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly
            420                 425                 430

GCG CAG ACC GAC GGC AAG TTC CTG CTG AGG CCG CGG AAG GAG CAG GGC     1344
Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg Lys Glu Gln Gly
        435                 440                 445

ACA TAC GCC CTG TCC CTC ATC TAT GGG AAG ACG GTG TAC CAC TAC CTC     1392
Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu
    450                 455                 460

ATC AGC CAA GAC AAG GCG GGC AAG TAC TGC ATT CCC GAG GGC ACC AAG     1440
Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys
465                 470                 475                 480

TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC     1488
Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp
                485                 490                 495
```

GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGT GCC AGC 1536
Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser
500 505 510

AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG 1584
Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr
515 520 525

TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC TCA GAT GGA TAC 1632
Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr
530 535 540

ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA CCG CGG CCG ATG 1680
Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys Pro Arg Pro Met
545 550 555 560

CCC ATG GAC ACG AGC GTG TAT GAG AGC CCC TAC AGC GAC CCA GAG GAG 1728
Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp Pro Glu Glu
565 570 575

CTC AAG GAC AAG AAG CTC TTC CTG AAG CGC GAT AAC CTC CTC ATA GCT 1776
Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
580 585 590

GAC ATT GAA CTT GGC TGC GGC AAC TTT GGC TCA GTG CGC CAG GGC GTG 1824
Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
595 600 605

TAC CGC ATG CGC AAG AAG CAG ATC GAC GTG GCC ATC AAG GTG CTG AAG 1872
Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
610 615 620

CAG GGC ACG GAG AAG GCA GAC ACG GAA GAG ATG ATG CGC GAG GCG CAG 1920
Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
625 630 635 640

ATC ATG CAC CAG CTG GAC AAC CCC TAC ATC GTG CGG CTC ATT GGC GTC 1968
Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
645 650 655

TGC CAG GCC GAG GCC CTC ATG CTG GTC ATG GAG ATG GCT GGG GGC GGG 2016
Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
660 665 670

CCG CTG CAC AAG TTC CTG GTC GGC AAG AGG GAG GAG ATC CCT GTG AGC 2064
Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
675 680 685

AAT GTG GCC GAG CTG CTG CAC CAG GTG TCC ATG GGG ATG AAG TAC CTG 2112
Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
690 695 700

GAG GAG AAG AAC TTT GTG CAC CGT GAC CTG GCG GCC CGC AAC GTC CTG 2160
Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
705 710 715 720

CTG GTT AAC CGG CAC TAC GCC AAG ATC AGC GAC TTT GGC CTC TCC AAA 2208

```
Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
                725                 730                 735

GCA CTG GGT GCC GAC GAC AGC TAC TAC ACT GCC CGC TCA GCA GGG AAG      2256
Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
            740                 745                 750

TGG CCG CTC AAG TGG TAC GCA CCC GAA TGC ATC AAC TTC CGC AAG TTC      2304
Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
        755                 760                 765

TCC AGC CGC AGC GAT GTC TGG AGC TAT GGG GTC ACC ATG TGG GAG GCC      2352
Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
    770                 775                 780

TTG TCC TAC GGC CAG AAG CCC TAC AAG AAG ATG AAA GGG CCG GAG GTC      2400
Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
785                 790                 795                 800

ATG GCC TTC ATC GAG CAG GGC AAG CGG ATG GAG TGC CCA CCA GAG TGT      2448
Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
                805                 810                 815

CCA CCC GAA CTG TAC GCA CTC ATG AGT GAC TGC TGG ATC TAC AAG TGG      2496
Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
            820                 825                 830

GAG GAT CGC CCC GAC TTC CTG ACC GTG GAG CAG CGC ATG CGA GCC TGT      2544
Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
        835                 840                 845

TAC TAC AGC CTG GCC AGC AAG GTG GAA GGG CCC CCA GGC AGC ACA CAG      2592
Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
    850                 855                 860

AAG GCT GAG GCT GCC TGT GCC TGA                                      2616
Lys Ala Glu Ala Ala Cys Ala
865                 870
```

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 871 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
```

35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Ala Met Pro Asp Pro
245 250 255
Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala
260 265 270
Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly Leu Phe Leu Leu
275 280 285
Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His
290 295 300
Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln Leu Asn Gly Thr
305 310 315 320
Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro Ala Glu Leu Cys
325 330 335
Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys
340 345 350
Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro Gly Val Phe Asp
355 360 365
Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg Gln Thr Trp Lys
370 375 380
Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln
385 390 395 400
Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr
405 410 415
His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly
420 425 430
Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg Lys Glu Gln Gly
435 440 445
Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu
450 455 460
Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys
465 470 475 480
Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp
485 490 495
Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser

500 505 510
Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr
515 520 525
Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr
530 535 540
Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys Pro Arg Pro Met
545 550 555 560
Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp Pro Glu Glu
565 570 575
Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
580 585 590
Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
595 600 605
Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
610 615 620
Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
625 630 635 640
Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
645 650 655
Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
660 665 670
Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
675 680 685
Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
690 695 700
Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
705 710 715 720
Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
725 730 735
Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
740 745 750
Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
755 760 765
Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
770 775 780
Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
785 790 795 800
Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
805 810 815
Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
820 825 830
Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
835 840 845
Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
850 855 860
Lys Ala Glu Ala Ala Cys Ala
865 870

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2598 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2595
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

ATG CCA GAC CCC GCG GCG CAC CTG CCC TTC TTC TAC GGC AGC ATC TCG 48
Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser
1 5 10 15

CGT GCC GAG GCC GAG GAG CAC CTG AAG CTG GCG GGC ATG GCG GAC GGG 96
Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
20 25 30

CTC TTC CTG CTG CGC CAG TGC CTG CGC TCG CTG GGC GGC TAT GTG CTG 144
Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
35 40 45

TCG CTC GTG CAC GAT GTG CGC TTC CAC CAC TTT CCC ATC GAG CGC CAG 192
Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
50 55 60

CTC AAC GGC ACC TAC GCC ATT GCC GGC GGC AAA GCG CAC TGT GGA CCG 240
Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
65 70 75 80

GCA GAG CTC TGC GAG TTC TAC TCG CGC GAC CCC GAC GGG CTG CCC TGC 288
Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys
85 90 95

AAC CTG CGC AAG CCG TGC AAC CGG CCG TCG GGC CTC GAG CCG CAG CCG 336
Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
100 105 110

GGG GTC TTC GAC TGC CTG CGA GAC GCC ATG GTG CGT GAC TAC GTG CGC 384
Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
115 120 125

CAG ACG TGG AAG CTG GAG GGC GAG GCC CTG GAG CAG GCC ATC ATC AGC 432
Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
130 135 140

CAG GCC CCG CAG GTG GAG AAG CTC ATT GCT ACG ACG GCC CAC GAG CGG 480
Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
145 150 155 160

ATG CCC TGG TAC CAC AGC AGC CTG ACG CGT GAG GAG GCC GAG CGC AAA 528
Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
165 170 175

CTT TAC TCT GGG GCG CAG ACC GAC GGC AAG TTC CTG CTG AGG CCG CGG 576
Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
180 185 190

AAG GAG CAG GGC ACA TAC GCC CTG TCC CTC ATC TAT GGG AAG ACG GTG 624
Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
195 200 205

TAC CAC TAC CTC ATC AGC CAA GAC AAG GCG GGC AAG TAC TGC ATT CCC 672
Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
210 215 220

GAG GGC ACC AAG TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG 720
Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
225 230 235 240

CTG AAG GCG GAC GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC 768
Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
245 250 255

AGC AGT GCC AGC AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC 816
Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
260 265 270

CAC CCA TCC ACG TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC 864
His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
275 280 285

TCA GAT GGA TAC ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA 912
Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
290 295 300

CCG CGG CCG ATG CCC ATG GAC ACG AGC GTG TAT GAG AGC CCC TAC AGC 960
Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
305 310 315 320

GAC CCA GAG GAG CTC AAG GAC AAG AAG CTC TTC CTG AAG CGC GAT AAC 1008
Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn
325 330 335

CTC CTC ATA GCT GAC ATT GAA CTT GGC TGC GGC AAC TTT GGC TCA GTG 1056
Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val
340 345 350

CGC CAG GGC GTG TAC CGC ATG CGC AAG AAG CAG ATC GAC GTG GCC ATC 1104
Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile
355 360 365

AAG GTG CTG AAG CAG GGC ACG GAG AAG GCA GAC ACG GAA GAG ATG ATG 1152
Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met
370 375 380

CGC GAG GCG CAG ATC ATG CAC CAG CTG GAC AAC CCC TAC ATC GTG CGG 1200
Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg
385 390 395 400

CTC ATT GGC GTC TGC CAG GCC GAG GCC CTC ATG CTG GTC ATG GAG ATG 1248
Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met
405 410 415

GCT GGG GGC GGG CCG CTG CAC AAG TTC CTG GTC GGC AAG AGG GAG GAG 1296
Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu
420 425 430

ATC CCT GTG AGC AAT GTG GCC GAG CTG CTG CAC CAG GTG TCC ATG GGG 1344

```
Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly
        435                 440                 445

ATG AAG TAC CTG GAG GAG AAG AAC TTT GTG CAC CGT GAC CTG GCG GCC     1392
Met Lys Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala
    450                 455                 460

CGC AAC GTC CTG CTG GTT AAC CGG CAC TAC GCC AAG ATC AGC GAC TTT     1440
Arg Asn Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe
465                 470                 475                 480

GGC CTC TCC AAA GCA CTG GGT GCC GAC GAC AGC TAC TAC ACT GCC CGC     1488
Gly Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg
                485                 490                 495

TCA GCA GGG AAG TGG CCG CTC AAG TGG TAC GCA CCC GAA TGC ATC AAC     1536
Ser Ala Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn
            500                 505                 510

TTC CGC AAG TTC TCC AGC CGC AGC GAT GTC TGG AGC TAT GGG GTC ACC     1584
Phe Arg Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr
        515                 520                 525

ATG TGG GAG GCC TTG TCC TAC GGC CAG AAG CCC TAC AAG AAG ATG AAA     1632
Met Trp Glu Ala Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys
    530                 535                 540

GGG CCG GAG GTC ATG GCC TTC ATC GAG CAG GGC AAG CGG ATG GAG TGC     1680
Gly Pro Glu Val Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys
545                 550                 555                 560

CCA CCA GAG TGT CCA CCC GAA CTG TAC GCA CTC ATG AGT GAC TGC TGG     1728
Pro Pro Glu Cys Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp
                565                 570                 575

ATC TAC AAG TGG GAG GAT CGC CCC GAC TTC CTG ACC GTG GAG CAG CGC     1776
Ile Tyr Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg
            580                 585                 590

ATG CGA GCC TGT TAC TAC AGC CTG GCC AGC AAG GTG GAA GGG CCC CCA     1824
Met Arg Ala Cys Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro
        595                 600                 605

GGC AGC ACA CAG AAG GCT GAG GCT GCC TGT GCC TGG GAT CCA CCG GTC     1872
Gly Ser Thr Gln Lys Ala Glu Ala Ala Cys Ala Trp Asp Pro Pro Val
    610                 615                 620

GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC     1920
Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
625                 630                 635                 640

ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG     1968
Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val
                645                 650                 655

TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG     2016
Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
            660                 665                 670
```

```
TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG     2064
Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
        675                 680                 685

ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC     2112
Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
    690                 695                 700

ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC     2160
Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
705                 710                 715                 720

CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC     2208
Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg
                725                 730                 735

GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG     2256
Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
            740                 745                 750

AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG     2304
Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu
        755                 760                 765

GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG     2352
Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln
    770                 775                 780

AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC     2400
Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp
785                 790                 795                 800

GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC     2448
Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
                805                 810                 815

GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC     2496
Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
            820                 825                 830

GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG     2544
Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu
        835                 840                 845

GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC     2592
Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr
    850                 855                 860

AAG TAA                                                              2598
Lys
865
```

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 865 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

```
Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser
 1               5                  10                  15
Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
            20                  25                  30
Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
        35                  40                  45
Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
    50                  55                  60
Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
65                  70                  75                  80
Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys
                85                  90                  95
Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
            100                 105                 110
Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
        115                 120                 125
Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
    130                 135                 140
Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
145                 150                 155                 160
Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
                165                 170                 175
Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
            180                 185                 190
Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
        195                 200                 205
Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
    210                 215                 220
Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
225                 230                 235                 240
Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
                245                 250                 255
Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
            260                 265                 270
His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
        275                 280                 285
Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
    290                 295                 300
Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
305                 310                 315                 320
Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn
                325                 330                 335
Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val
            340                 345                 350
Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile
        355                 360                 365
Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met
    370                 375                 380
Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg
```

385 390 395 400
Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met
405 410 415
Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu
420 425 430
Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly
435 440 445
Met Lys Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala
450 455 460
Arg Asn Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe
465 470 475 480
Gly Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg
485 490 495
Ser Ala Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn
500 505 510
Phe Arg Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr
515 520 525
Met Trp Glu Ala Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys
530 535 540
Gly Pro Glu Val Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys
545 550 555 560
Pro Pro Glu Cys Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp
565 570 575
Ile Tyr Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg
580 585 590
Met Arg Ala Cys Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro
595 600 605
Gly Ser Thr Gln Lys Ala Glu Ala Ala Cys Ala Trp Asp Pro Pro Val
610 615 620
Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
625 630 635 640
Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val
645 650 655
Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
660 665 670
Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
675 680 685
Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
690 695 700
Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
705 710 715 720
Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg
725 730 735
Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
740 745 750
Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu
755 760 765
Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln
770 775 780
Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp
785 790 795 800
Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
805 810 815
Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
820 825 830
Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu
835 840 845
Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr

850 855 860
Lys
865

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1635 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1632
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

ATG GAG AAC TTC CAA AAG GTG GAA AAG ATC GGA GAG GGC ACG TAC GGA 48
Met Glu Asn Phe Gln Lys Val Glu Lys Ile Gly Glu Gly Thr Tyr Gly
1 5 10 15

GTT GTG TAC AAA GCC AGA AAC AAG TTG ACG GGA GAG GTG GTG GCG CTT 96
Val Val Tyr Lys Ala Arg Asn Lys Leu Thr Gly Glu Val Val Ala Leu
20 25 30

AAG AAA ATC CGC CTG GAC ACT GAG ACT GAG GGT GTG CCC AGT ACT GCC 144
Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu Gly Val Pro Ser Thr Ala
35 40 45

ATC CGA GAG ATC TCT CTG CTT AAG GAG CTT AAC CAT CCT AAT ATT GTC 192
Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Asn His Pro Asn Ile Val
50 55 60

AAG CTG CTG GAT GTC ATT CAC ACA GAA AAT AAA CTC TAC CTG GTT TTT 240
Lys Leu Leu Asp Val Ile His Thr Glu Asn Lys Leu Tyr Leu Val Phe
65 70 75 80

GAA TTT CTG CAC CAA GAT CTC AAG AAA TTC ATG GAT GCC TCT GCT CTC 288
Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu
85 90 95

ACT GGC ATT CCT CTT CCC CTC ATC AAG AGC TAT CTG TTC CAG CTG CTC 336
Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser Tyr Leu Phe Gln Leu Leu
100 105 110

CAG GGC CTA GCT TTC TGC CAT TCT CAT CGG GTC CTC CAC CGA GAC CTT 384
Gln Gly Leu Ala Phe Cys His Ser His Arg Val Leu His Arg Asp Leu
115 120 125

AAA CCT CAG AAT CTG CTT ATT AAC ACA GAG GGG GCC ATC AAG CTA GCA 432
Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys Leu Ala
130 135 140

GAC TTT GGA CTA GCC AGA GCT TTT GGA GTC CCT GTT CGT ACT TAC ACC 480

Asp Phe Gly Leu Ala Arg Ala Phe Gly Val Pro Val Arg Thr Tyr Thr
145 150 155 160

CAT GAG GTG GTG ACC CTG TGG TAC CGA GCT CCT GAA ATC CTC CTG GGC 528
His Glu Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Ile Leu Leu Gly
165 170 175

TCG AAA TAT TAT TCC ACA GCT GTG GAC ATC TGG AGC CTG GGC TGC ATC 576
Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile Trp Ser Leu Gly Cys Ile
180 185 190

TTT GCT GAG ATG GTG ACT CGC CGG GCC CTG TTC CCT GGA GAT TCT GAG 624
Phe Ala Glu Met Val Thr Arg Arg Ala Leu Phe Pro Gly Asp Ser Glu
195 200 205

ATT GAC CAG CTC TTC CGG ATC TTT CGG ACT CTG GGG ACC CCA GAT GAG 672
Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr Leu Gly Thr Pro Asp Glu
210 215 220

GTG GTG TGG CCA GGA GTT ACT TCT ATG CCT GAT TAC AAG CCA AGT TTC 720
Val Val Trp Pro Gly Val Thr Ser Met Pro Asp Tyr Lys Pro Ser Phe
225 230 235 240

CCC AAG TGG GCC CGG CAA GAT TTT AGT AAA GTT GTA CCT CCC CTG GAT 768
Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys Val Val Pro Pro Leu Asp
245 250 255

GAA GAT GGA CGG AGC TTG TTA TCG CAA ATG CTG CAC TAC GAC CCT AAC 816
Glu Asp Gly Arg Ser Leu Leu Ser Gln Met Leu His Tyr Asp Pro Asn
260 265 270

AAG CGG ATT TCG GCC AAG GCA GCC CTG GCT CAC CCT TTC TTC CAG GAT 864
Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala His Pro Phe Phe Gln Asp
275 280 285

GTG ACC AAG CCA GTA CCC CAT CTT CGA CTC TGG GAT CCA CCG GTC GCC 912
Val Thr Lys Pro Val Pro His Leu Arg Leu Trp Asp Pro Pro Val Ala
290 295 300

ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC 960
Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile
305 310 315 320

CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC 1008
Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser
325 330 335

GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC 1056
Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe
340 345 350

ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC 1104
Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr
355 360 365

ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG 1152
Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met
370 375 380

AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG 1200
Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln
385 390 395 400

GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC 1248
Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala
405 410 415

GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG 1296
Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys
420 425 430

GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG 1344
Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu
435 440 445

TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG 1392
Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys
450 455 460

AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC 1440
Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly
465 470 475 480

AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC 1488
Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp
485 490 495

GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC 1536
Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala
500 505 510

CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG 1584
Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu
515 520 525

TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG T 1633
Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
530 535 540

AA 1635

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 544 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Met Glu Asn Phe Gln Lys Val Glu Lys Ile Gly Glu Gly Thr Tyr Gly
1 5 10 15

Val Val Tyr Lys Ala Arg Asn Lys Leu Thr Gly Glu Val Val Ala Leu
20 25 30
Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu Gly Val Pro Ser Thr Ala
35 40 45
Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Asn His Pro Asn Ile Val
50 55 60
Lys Leu Leu Asp Val Ile His Thr Glu Asn Lys Leu Tyr Leu Val Phe
65 70 75 80
Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu
85 90 95
Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser Tyr Leu Phe Gln Leu Leu
100 105 110
Gln Gly Leu Ala Phe Cys His Ser His Arg Val Leu His Arg Asp Leu
115 120 125
Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys Leu Ala
130 135 140
Asp Phe Gly Leu Ala Arg Ala Phe Gly Val Pro Val Arg Thr Tyr Thr
145 150 155 160
His Glu Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Ile Leu Leu Gly
165 170 175
Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile Trp Ser Leu Gly Cys Ile
180 185 190
Phe Ala Glu Met Val Thr Arg Arg Ala Leu Phe Pro Gly Asp Ser Glu
195 200 205
Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr Leu Gly Thr Pro Asp Glu
210 215 220
Val Val Trp Pro Gly Val Thr Ser Met Pro Asp Tyr Lys Pro Ser Phe
225 230 235 240
Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys Val Val Pro Pro Leu Asp
245 250 255
Glu Asp Gly Arg Ser Leu Leu Ser Gln Met Leu His Tyr Asp Pro Asn
260 265 270
Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala His Pro Phe Phe Gln Asp
275 280 285
Val Thr Lys Pro Val Pro His Leu Arg Leu Trp Asp Pro Pro Val Ala
290 295 300
Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile
305 310 315 320
Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser
325 330 335
Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe
340 345 350
Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr
355 360 365
Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met
370 375 380
Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln
385 390 395 400
Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala
405 410 415
Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys
420 425 430
Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu
435 440 445
Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys
450 455 460
Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly
465 470 475 480

```
Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp
            485                 490                 495
Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala
        500                 505                 510
Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu
    515                 520                 525
Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
530                 535                 540
```

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1635 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1632
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

```
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG      48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC      96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC     144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC     192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG     240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG     288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG     336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC     384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
```

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCC ATG GAG AAC TTC CAA AAG GTG GAA AAG ATC 768
Gly Leu Arg Ser Arg Ala Met Glu Asn Phe Gln Lys Val Glu Lys Ile
245 250 255

GGA GAG GGC ACG TAC GGA GTT GTG TAC AAA GCC AGA AAC AAG TTG ACG 816
Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr
260 265 270

GGA GAG GTG GTG GCG CTT AAG AAA ATC CGC CTG GAC ACT GAG ACT GAG 864
Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu
275 280 285

GGT GTG CCC AGT ACT GCC ATC CGA GAG ATC TCT CTG CTT AAG GAG CTT 912
Gly Val Pro Ser Thr Ala Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu
290 295 300

AAC CAT CCT AAT ATT GTC AAG CTG CTG GAT GTC ATT CAC ACA GAA AAT 960
Asn His Pro Asn Ile Val Lys Leu Leu Asp Val Ile His Thr Glu Asn
305 310 315 320

AAA CTC TAC CTG GTT TTT GAA TTT CTG CAC CAA GAT CTC AAG AAA TTC 1008
Lys Leu Tyr Leu Val Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe
325 330 335

ATG GAT GCC TCT GCT CTC ACT GGC ATT CCT CTT CCC CTC ATC AAG AGC 1056
Met Asp Ala Ser Ala Leu Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser
340 345 350

TAT CTG TTC CAG CTG CTC CAG GGC CTA GCT TTC TGC CAT TCT CAT CGG 1104
Tyr Leu Phe Gln Leu Leu Gln Gly Leu Ala Phe Cys His Ser His Arg

355 360 365

GTC CTC CAC CGA GAC CTT AAA CCT CAG AAT CTG CTT ATT AAC ACA GAG 1152
Val Leu His Arg Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu
370 375 380

GGG GCC ATC AAG CTA GCA GAC TTT GGA CTA GCC AGA GCT TTT GGA GTC 1200
Gly Ala Ile Lys Leu Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Val
385 390 395 400

CCT GTT CGT ACT TAC ACC CAT GAG GTG GTG ACC CTG TGG TAC CGA GCT 1248
Pro Val Arg Thr Tyr Thr His Glu Val Val Thr Leu Trp Tyr Arg Ala
405 410 415

CCT GAA ATC CTC CTG GGC TCG AAA TAT TAT TCC ACA GCT GTG GAC ATC 1296
Pro Glu Ile Leu Leu Gly Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile
420 425 430

TGG AGC CTG GGC TGC ATC TTT GCT GAG ATG GTG ACT CGC CGG GCC CTG 1344
Trp Ser Leu Gly Cys Ile Phe Ala Glu Met Val Thr Arg Arg Ala Leu
435 440 445

TTC CCT GGA GAT TCT GAG ATT GAC CAG CTC TTC CGG ATC TTT CGG ACT 1392
Phe Pro Gly Asp Ser Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr
450 455 460

CTG GGG ACC CCA GAT GAG GTG GTG TGG CCA GGA GTT ACT TCT ATG CCT 1440
Leu Gly Thr Pro Asp Glu Val Val Trp Pro Gly Val Thr Ser Met Pro
465 470 475 480

GAT TAC AAG CCA AGT TTC CCC AAG TGG GCC CGG CAA GAT TTT AGT AAA 1488
Asp Tyr Lys Pro Ser Phe Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys
485 490 495

GTT GTA CCT CCC CTG GAT GAA GAT GGA CGG AGC TTG TTA TCG CAA ATG 1536
Val Val Pro Pro Leu Asp Glu Asp Gly Arg Ser Leu Leu Ser Gln Met
500 505 510

CTG CAC TAC GAC CCT AAC AAG CGG ATT TCG GCC AAG GCA GCC CTG GCT 1584
Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala
515 520 525

CAC CCT TTC TTC CAG GAT GTG ACC AAG CCA GTA CCC CAT CTT CGA CTC T 1633
His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu
530 535 540

GA 1635

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 544 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1   5   10   15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20   25   30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35   40   45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50   55   60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65   70   75   80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85   90   95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100   105   110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115   120   125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130   135   140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145   150   155   160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165   170   175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180   185   190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195   200   205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210   215   220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225   230   235   240
Gly Leu Arg Ser Arg Ala Met Glu Asn Phe Gln Lys Val Glu Lys Ile
                245   250   255
Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr
            260   265   270
Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu
        275   280   285
Gly Val Pro Ser Thr Ala Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu
    290   295   300
Asn His Pro Asn Ile Val Lys Leu Leu Asp Val Ile His Thr Glu Asn
305   310   315   320
Lys Leu Tyr Leu Val Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe
                325   330   335
Met Asp Ala Ser Ala Leu Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser
            340   345   350
Tyr Leu Phe Gln Leu Leu Gln Gly Leu Ala Phe Cys His Ser His Arg
        355   360   365
Val Leu His Arg Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu
    370   375   380
Gly Ala Ile Lys Leu Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Val
385   390   395   400
Pro Val Arg Thr Tyr Thr His Glu Val Val Thr Leu Trp Tyr Arg Ala
                405   410   415
Pro Glu Ile Leu Leu Gly Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile
            420   425   430
Trp Ser Leu Gly Cys Ile Phe Ala Glu Met Val Thr Arg Arg Ala Leu

```
        435                 440                 445
Phe Pro Gly Asp Ser Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr
    450                 455                 460
Leu Gly Thr Pro Asp Glu Val Val Trp Pro Gly Val Thr Ser Met Pro
465                 470                 475                 480
Asp Tyr Lys Pro Ser Phe Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys
                485                 490                 495
Val Val Pro Pro Leu Asp Glu Asp Gly Arg Ser Leu Leu Ser Gln Met
            500                 505                 510
Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala
        515                 520                 525
His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu
    530                 535                 540
```

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2532 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2529
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

```
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG        48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC        96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC       144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC       192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG       240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG       288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG       336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
```

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GAG ATG CTG TCC CGT GGG TGG TTT CAC CGA GAC 768
Gly Leu Arg Ser Arg Glu Met Leu Ser Arg Gly Trp Phe His Arg Asp
245 250 255

CTC AGT GGG CTG GAT GCA GAG ACC CTG CTC AAG GGC CGA GGT GTC CAC 816
Leu Ser Gly Leu Asp Ala Glu Thr Leu Leu Lys Gly Arg Gly Val His
260 265 270

GGT AGC TTC CTG GCT CGG CCC AGT CGC AAG AAC CAG GGT GAC TTC TCG 864
Gly Ser Phe Leu Ala Arg Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser
275 280 285

CTC TCC GTC AGG GTG GGG GAT CAG GTG ACC CAT ATT CGG ATC CAG AAC 912
Leu Ser Val Arg Val Gly Asp Gln Val Thr His Ile Arg Ile Gln Asn
290 295 300

TCA GGG GAT TTC TAT GAC CTG TAT GGA GGG GAG AAG TTT GCG ACT CTG 960
Ser Gly Asp Phe Tyr Asp Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu
305 310 315 320

ACA GAG CTG GTG GAG TAC TAC ACT CAG CAG CAG GGT GTC CTG CAG GAC 1008
Thr Glu Leu Val Glu Tyr Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp
325 330 335

CGC GAC GGC ACC ATC ATC CAC CTC AAG TAC CCG CTG AAC TGC TCC GAT 1056

Arg Asp Gly Thr Ile Ile His Leu Lys Tyr Pro Leu Asn Cys Ser Asp
340 345 350

CCC ACT AGT GAG AGG TGG TAC CAT GGC CAC ATG TCT GGC GGG CAG GCA 1104
Pro Thr Ser Glu Arg Trp Tyr His Gly His Met Ser Gly Gly Gln Ala
355 360 365

GAG ACG CTG CTG CAG GCC AAG GGC GAG CCC TGG ACG TTT CTT GTG CGT 1152
Glu Thr Leu Leu Gln Ala Lys Gly Glu Pro Trp Thr Phe Leu Val Arg
370 375 380

GAG AGC CTC AGC CAG CCT GGA GAC TTC GTG CTT TCT GTG CTC AGT GAC 1200
Glu Ser Leu Ser Gln Pro Gly Asp Phe Val Leu Ser Val Leu Ser Asp
385 390 395 400

CAG CCC AAG GCT GGC CCA GGC TCC CCG CTC AGG GTC ACC CAC ATC AAG 1248
Gln Pro Lys Ala Gly Pro Gly Ser Pro Leu Arg Val Thr His Ile Lys
405 410 415

GTC ATG TGC GAG GGT GGA CGC TAC ACA GTG GGT GGT TTG GAG ACC TTC 1296
Val Met Cys Glu Gly Gly Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe
420 425 430

GAC AGC CTC ACG GAC CTG GTA GAG CAT TTC AAG AAG ACG GGG ATT GAG 1344
Asp Ser Leu Thr Asp Leu Val Glu His Phe Lys Lys Thr Gly Ile Glu
435 440 445

GAG GCC TCA GGC GCC TTT GTC TAC CTG CGG CAG CCG TAC TAT GCC ACG 1392
Glu Ala Ser Gly Ala Phe Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr
450 455 460

AGG GTG AAT GCG GCT GAC ATT GAG AAC CGA GTG TTG GAA CTG AAC AAG 1440
Arg Val Asn Ala Ala Asp Ile Glu Asn Arg Val Leu Glu Leu Asn Lys
465 470 475 480

AAG CAG GAG TCC GAG GAT ACA GCC AAG GCT GGC TTC TGG GAG GAG TTT 1488
Lys Gln Glu Ser Glu Asp Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe
485 490 495

GAG AGT TTG CAG AAG CAG GAG GTG AAG AAC TTG CAC CAG CGT CTG GAA 1536
Glu Ser Leu Gln Lys Gln Glu Val Lys Asn Leu His Gln Arg Leu Glu
500 505 510

GGG CAG CGG CCA GAG AAC AAG GGC AAG AAC CGC TAC AAG AAC ATT CTC 1584
Gly Gln Arg Pro Glu Asn Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu
515 520 525

CCC TTT GAC CAC AGC CGA GTG ATC CTG CAG GGA CGG GAC AGT AAC ATC 1632
Pro Phe Asp His Ser Arg Val Ile Leu Gln Gly Arg Asp Ser Asn Ile
530 535 540

CCC GGG TCC GAC TAC ATC AAT GCC AAC TAC ATC AAG AAC CAG CTG CTA 1680
Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu
545 550 555 560

GGC CCT GAT GAG AAC GCT AAG ACC TAC ATC GCC AGC CAG GGC TGT CTG 1728
Gly Pro Asp Glu Asn Ala Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu
565 570 575

```
GAG GCC ACG GTC AAT GAC TTC TGG CAG ATG GCG TGG CAG GAG AAC AGC      1776
Glu Ala Thr Val Asn Asp Phe Trp Gln Met Ala Trp Gln Glu Asn Ser
            580                 585                 590

CGT GTC ATC GTC ATG ACC ACC CGA GAG GTG GAG AAA GGC CGG AAC AAA      1824
Arg Val Ile Val Met Thr Thr Arg Glu Val Glu Lys Gly Arg Asn Lys
        595                 600                 605

TGC GTC CCA TAC TGG CCC GAG GTG GGC ATG CAG CGT GCT TAT GGG CCC      1872
Cys Val Pro Tyr Trp Pro Glu Val Gly Met Gln Arg Ala Tyr Gly Pro
    610                 615                 620

TAC TCT GTG ACC AAC TGC GGG GAG CAT GAC ACA ACC GAA TAC AAA CTC      1920
Tyr Ser Val Thr Asn Cys Gly Glu His Asp Thr Thr Glu Tyr Lys Leu
625                 630                 635                 640

CGT ACC TTA CAG GTC TCC CCG CTG GAC AAT GGA GAC CTG ATT CGG GAG      1968
Arg Thr Leu Gln Val Ser Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu
                645                 650                 655

ATC TGG CAT TAC CAG TAC CTG AGC TGG CCC GAC CAT GGG GTC CCC AGT      2016
Ile Trp His Tyr Gln Tyr Leu Ser Trp Pro Asp His Gly Val Pro Ser
            660                 665                 670

GAG CCT GGG GGT GTC CTC AGC TTC CTG GAC CAG ATC AAC CAG CGG CAG      2064
Glu Pro Gly Gly Val Leu Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln
        675                 680                 685

GAA AGT CTG CCT CAC GCA GGG CCC ATC ATC GTG CAC TGC AGC GCC GGC      2112
Glu Ser Leu Pro His Ala Gly Pro Ile Ile Val His Cys Ser Ala Gly
    690                 695                 700

ATC GGC CGC ACA GGC ACC ATC ATT GTC ATC GAC ATG CTC ATG GAG AAC      2160
Ile Gly Arg Thr Gly Thr Ile Ile Val Ile Asp Met Leu Met Glu Asn
705                 710                 715                 720

ATC TCC ACC AAG GGC CTG GAC TGT GAC ATT GAC ATC CAG AAG ACC ATC      2208
Ile Ser Thr Lys Gly Leu Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile
                725                 730                 735

CAG ATG GTG CGG GCG CAG CGC TCG GGC ATG GTG CAG ACG GAG GCG CAG      2256
Gln Met Val Arg Ala Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln
            740                 745                 750

TAC AAG TTC ATC TAC GTG GCC ATC GCC CAG TTC ATT GAA ACC ACT AAG      2304
Tyr Lys Phe Ile Tyr Val Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys
        755                 760                 765

AAG AAG CTG GAG GTC CTG CAG TCG CAG AAG GGC CAG GAG TCG GAG TAC      2352
Lys Lys Leu Glu Val Leu Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr
    770                 775                 780

GGG AAC ATC ACC TAT CCC CCA GCC ATG AAG AAT GCC CAT GCC AAG GCC      2400
Gly Asn Ile Thr Tyr Pro Pro Ala Met Lys Asn Ala His Ala Lys Ala
785                 790                 795                 800

TCC CGC ACC TCG TCC AAA CAC AAG GAG GAT GTG TAT GAG AAC CTG CAC      2448
```

```
Ser Arg Thr Ser Ser Lys His Lys Glu Asp Val Tyr Glu Asn Leu His
                805                 810                 815

ACT AAG AAC AAG AGG GAG GAG AAA GTG AAG AAG CAG CGG TCA GCA GAC     2496
Thr Lys Asn Lys Arg Glu Glu Lys Val Lys Lys Gln Arg Ser Ala Asp
            820                 825                 830

AAG GAG AAG AGC AAG GGT TCC CTC AAG AGG AAG TGA                      2532
Lys Glu Lys Ser Lys Gly Ser Leu Lys Arg Lys
        835                 840
```

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 843 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Arg Glu Met Leu Ser Arg Gly Trp Phe His Arg Asp
                245                 250                 255
Leu Ser Gly Leu Asp Ala Glu Thr Leu Leu Lys Gly Arg Gly Val His
```

260 265 270
Gly Ser Phe Leu Ala Arg Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser
275 280 285
Leu Ser Val Arg Val Gly Asp Gln Val Thr His Ile Arg Ile Gln Asn
290 295 300
Ser Gly Asp Phe Tyr Asp Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu
305 310 315 320
Thr Glu Leu Val Glu Tyr Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp
325 330 335
Arg Asp Gly Thr Ile Ile His Leu Lys Tyr Pro Leu Asn Cys Ser Asp
340 345 350
Pro Thr Ser Glu Arg Trp Tyr His Gly His Met Ser Gly Gly Gln Ala
355 360 365
Glu Thr Leu Leu Gln Ala Lys Gly Glu Pro Trp Thr Phe Leu Val Arg
370 375 380
Glu Ser Leu Ser Gln Pro Gly Asp Phe Val Leu Ser Val Leu Ser Asp
385 390 395 400
Gln Pro Lys Ala Gly Pro Gly Ser Pro Leu Arg Val Thr His Ile Lys
405 410 415
Val Met Cys Glu Gly Gly Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe
420 425 430
Asp Ser Leu Thr Asp Leu Val Glu His Phe Lys Lys Thr Gly Ile Glu
435 440 445
Glu Ala Ser Gly Ala Phe Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr
450 455 460
Arg Val Asn Ala Ala Asp Ile Glu Asn Arg Val Leu Glu Leu Asn Lys
465 470 475 480
Lys Gln Glu Ser Glu Asp Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe
485 490 495
Glu Ser Leu Gln Lys Gln Glu Val Lys Asn Leu His Gln Arg Leu Glu
500 505 510
Gly Gln Arg Pro Glu Asn Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu
515 520 525
Pro Phe Asp His Ser Arg Val Ile Leu Gln Gly Arg Asp Ser Asn Ile
530 535 540
Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu
545 550 555 560
Gly Pro Asp Glu Asn Ala Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu
565 570 575
Glu Ala Thr Val Asn Asp Phe Trp Gln Met Ala Trp Gln Glu Asn Ser
580 585 590
Arg Val Ile Val Met Thr Thr Arg Glu Val Glu Lys Gly Arg Asn Lys
595 600 605
Cys Val Pro Tyr Trp Pro Glu Val Gly Met Gln Arg Ala Tyr Gly Pro
610 615 620
Tyr Ser Val Thr Asn Cys Gly Glu His Asp Thr Thr Glu Tyr Lys Leu
625 630 635 640
Arg Thr Leu Gln Val Ser Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu
645 650 655
Ile Trp His Tyr Gln Tyr Leu Ser Trp Pro Asp His Gly Val Pro Ser
660 665 670
Glu Pro Gly Gly Val Leu Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln
675 680 685
Glu Ser Leu Pro His Ala Gly Pro Ile Ile Val His Cys Ser Ala Gly
690 695 700
Ile Gly Arg Thr Gly Thr Ile Ile Val Ile Asp Met Leu Met Glu Asn
705 710 715 720
Ile Ser Thr Lys Gly Leu Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile

```
                725                 730                 735
Gln Met Val Arg Ala Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln
            740                 745                 750
Tyr Lys Phe Ile Tyr Val Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys
        755                 760                 765
Lys Lys Leu Glu Val Leu Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr
    770                 775                 780
Gly Asn Ile Thr Tyr Pro Pro Ala Met Lys Asn Ala His Ala Lys Ala
785                 790                 795                 800
Ser Arg Thr Ser Ser Lys His Lys Glu Asp Val Tyr Glu Asn Leu His
                805                 810                 815
Thr Lys Asn Lys Arg Glu Glu Lys Val Lys Lys Gln Arg Ser Ala Asp
            820                 825                 830
Lys Glu Lys Ser Lys Gly Ser Leu Lys Arg Lys
        835                 840
```

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2562 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2559
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

```
ATG CTG TCC CGT GGG TGG TTT CAC CGA GAC CTC AGT GGG CTG GAT GCA      48
Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
 1               5                  10                  15

GAG ACC CTG CTC AAG GGC CGA GGT GTC CAC GGT AGC TTC CTG GCT CGG      96
Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
            20                  25                  30

CCC AGT CGC AAG AAC CAG GGT GAC TTC TCG CTC TCC GTC AGG GTG GGG     144
Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
        35                  40                  45

GAT CAG GTG ACC CAT ATT CGG ATC CAG AAC TCA GGG GAT TTC TAT GAC     192
Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
    50                  55                  60

CTG TAT GGA GGG GAG AAG TTT GCG ACT CTG ACA GAG CTG GTG GAG TAC     240
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
65                  70                  75                  80

TAC ACT CAG CAG CAG GGT GTC CTG CAG GAC CGC GAC GGC ACC ATC ATC     288
Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
                85                  90                  95

CAC CTC AAG TAC CCG CTG AAC TGC TCC GAT CCC ACT AGT GAG AGG TGG     336
```

His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
100 105 110

TAC CAT GGC CAC ATG TCT GGC GGG CAG GCA GAG ACG CTG CTG CAG GCC 384
Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
115 120 125

AAG GGC GAG CCC TGG ACG TTT CTT GTG CGT GAG AGC CTC AGC CAG CCT 432
Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
130 135 140

GGA GAC TTC GTG CTT TCT GTG CTC AGT GAC CAG CCC AAG GCT GGC CCA 480
Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
145 150 155 160

GGC TCC CCG CTC AGG GTC ACC CAC ATC AAG GTC ATG TGC GAG GGT GGA 528
Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
165 170 175

CGC TAC ACA GTG GGT GGT TTG GAG ACC TTC GAC AGC CTC ACG GAC CTG 576
Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
180 185 190

GTA GAG CAT TTC AAG AAG ACG GGG ATT GAG GAG GCC TCA GGC GCC TTT 624
Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
195 200 205

GTC TAC CTG CGG CAG CCG TAC TAT GCC ACG AGG GTG AAT GCG GCT GAC 672
Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
210 215 220

ATT GAG AAC CGA GTG TTG GAA CTG AAC AAG AAG CAG GAG TCC GAG GAT 720
Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
225 230 235 240

ACA GCC AAG GCT GGC TTC TGG GAG GAG TTT GAG AGT TTG CAG AAG CAG 768
Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
245 250 255

GAG GTG AAG AAC TTG CAC CAG CGT CTG GAA GGG CAG CGG CCA GAG AAC 816
Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
260 265 270

AAG GGC AAG AAC CGC TAC AAG AAC ATT CTC CCC TTT GAC CAC AGC CGA 864
Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
275 280 285

GTG ATC CTG CAG GGA CGG GAC AGT AAC ATC CCC GGG TCC GAC TAC ATC 912
Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
290 295 300

AAT GCC AAC TAC ATC AAG AAC CAG CTG CTA GGC CCT GAT GAG AAC GCT 960
Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala
305 310 315 320

AAG ACC TAC ATC GCC AGC CAG GGC TGT CTG GAG GCC ACG GTC AAT GAC 1008
Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp
325 330 335

TTC TGG CAG ATG GCG TGG CAG GAG AAC AGC CGT GTC ATC GTC ATG ACC 1056
Phe Trp Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr
340 345 350

ACC CGA GAG GTG GAG AAA GGC CGG AAC AAA TGC GTC CCA TAC TGG CCC 1104
Thr Arg Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro
355 360 365

GAG GTG GGC ATG CAG CGT GCT TAT GGG CCC TAC TCT GTG ACC AAC TGC 1152
Glu Val Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys
370 375 380

GGG GAG CAT GAC ACA ACC GAA TAC AAA CTC CGT ACC TTA CAG GTC TCC 1200
Gly Glu His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser
385 390 395 400

CCG CTG GAC AAT GGA GAC CTG ATT CGG GAG ATC TGG CAT TAC CAG TAC 1248
Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr
405 410 415

CTG AGC TGG CCC GAC CAT GGG GTC CCC AGT GAG CCT GGG GGT GTC CTC 1296
Leu Ser Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu
420 425 430

AGC TTC CTG GAC CAG ATC AAC CAG CGG CAG GAA AGT CTG CCT CAC GCA 1344
Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala
435 440 445

GGG CCC ATC ATC GTG CAC TGC AGC GCC GGC ATC GGC CGC ACA GGC ACC 1392
Gly Pro Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr
450 455 460

ATC ATT GTC ATC GAC ATG CTC ATG GAG AAC ATC TCC ACC AAG GGC CTG 1440
Ile Ile Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu
465 470 475 480

GAC TGT GAC ATT GAC ATC CAG AAG ACC ATC CAG ATG GTG CGG GCG CAG 1488
Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln
485 490 495

CGC TCG GGC ATG GTG CAG ACG GAG GCG CAG TAC AAG TTC ATC TAC GTG 1536
Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val
500 505 510

GCC ATC GCC CAG TTC ATT GAA ACC ACT AAG AAG AAG CTG GAG GTC CTG 1584
Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu
515 520 525

CAG TCG CAG AAG GGC CAG GAG TCG GAG TAC GGG AAC ATC ACC TAT CCC 1632
Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro
530 535 540

CCA GCC ATG AAG AAT GCC CAT GCC AAG GCC TCC CGC ACC TCG TCC AAA 1680
Pro Ala Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys
545 550 555 560

CAC AAG GAG GAT GTG TAT GAG AAC CTG CAC ACT AAG AAC AAG AGG GAG 1728

His Lys Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu
565 570 575

GAG AAA GTG AAG AAG CAG CGG TCA GCA GAC AAG GAG AAG AGC AAG GGT 1776
Glu Lys Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly
580 585 590

TCC CTC AAG AGG AAG CGA ATT CTG CAG TCG ACG GTA CCG CGG GCC CGG 1824
Ser Leu Lys Arg Lys Arg Ile Leu Gln Ser Thr Val Pro Arg Ala Arg
595 600 605

GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC 1872
Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr
610 615 620

GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC 1920
Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His
625 630 635 640

AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG 1968
Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys
645 650 655

CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG 2016
Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp
660 665 670

CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC 2064
Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg
675 680 685

TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC 2112
Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro
690 695 700

GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC 2160
Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn
705 710 715 720

TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC 2208
Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn
725 730 735

CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG 2256
Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu
740 745 750

GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG 2304
Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met
755 760 765

GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC 2352
Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His
770 775 780

AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC 2400
Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn
785 790 795 800

```
ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG     2448
Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu
                805                 810                 815

AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC     2496
Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His
            820                 825                 830

ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG     2544
Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met
        835                 840                 845

GAC GAG CTG TAC AAG TAA                                              2562
Asp Glu Leu Tyr Lys
    850
```

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 853 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

```
Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
 1               5                  10                  15
Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
            20                  25                  30
Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
        35                  40                  45
Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
    50                  55                  60
Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
65                  70                  75                  80
Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
                85                  90                  95
His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
            100                 105                 110
Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
        115                 120                 125
Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
    130                 135                 140
Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
145                 150                 155                 160
Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                165                 170                 175
Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
            180                 185                 190
Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
        195                 200                 205
Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
```

```
    210                 215                 220
Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
225                 230                 235                 240
Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
                245                 250                 255
Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
            260                 265                 270
Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
        275                 280                 285
Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
    290                 295                 300
Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala
305                 310                 315                 320
Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu Glu Ala Thr Val Asn Asp
                325                 330                 335
Phe Trp Gln Met Ala Trp Gln Glu Asn Ser Arg Val Ile Val Met Thr
            340                 345                 350
Thr Arg Glu Val Glu Lys Gly Arg Asn Lys Cys Val Pro Tyr Trp Pro
        355                 360                 365
Glu Val Gly Met Gln Arg Ala Tyr Gly Pro Tyr Ser Val Thr Asn Cys
    370                 375                 380
Gly Glu His Asp Thr Thr Glu Tyr Lys Leu Arg Thr Leu Gln Val Ser
385                 390                 395                 400
Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu Ile Trp His Tyr Gln Tyr
                405                 410                 415
Leu Ser Trp Pro Asp His Gly Val Pro Ser Glu Pro Gly Gly Val Leu
            420                 425                 430
Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln Glu Ser Leu Pro His Ala
        435                 440                 445
Gly Pro Ile Ile Val His Cys Ser Ala Gly Ile Gly Arg Thr Gly Thr
    450                 455                 460
Ile Ile Val Ile Asp Met Leu Met Glu Asn Ile Ser Thr Lys Gly Leu
465                 470                 475                 480
Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile Gln Met Val Arg Ala Gln
                485                 490                 495
Arg Ser Gly Met Val Gln Thr Glu Ala Gln Tyr Lys Phe Ile Tyr Val
            500                 505                 510
Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys Lys Lys Leu Glu Val Leu
        515                 520                 525
Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr Gly Asn Ile Thr Tyr Pro
    530                 535                 540
Pro Ala Met Lys Asn Ala His Ala Lys Ala Ser Arg Thr Ser Ser Lys
545                 550                 555                 560
His Lys Glu Asp Val Tyr Glu Asn Leu His Thr Lys Asn Lys Arg Glu
                565                 570                 575
Glu Lys Val Lys Lys Gln Arg Ser Ala Asp Lys Glu Lys Ser Lys Gly
            580                 585                 590
Ser Leu Lys Arg Lys Arg Ile Leu Gln Ser Thr Val Pro Arg Ala Arg
        595                 600                 605
Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr
    610                 615                 620
Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His
625                 630                 635                 640
Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys
                645                 650                 655
Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp
            660                 665                 670
Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg
```

675 680 685
Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro
690 695 700
Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn
705 710 715 720
Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn
725 730 735
Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu
740 745 750
Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met
755 760 765
Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His
770 775 780
Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn
785 790 795 800
Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu
805 810 815
Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His
820 825 830
Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met
835 840 845
Asp Glu Leu Tyr Lys
850

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2994 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2991
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC 768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro
245 250 255

CCG GGG CTG CGG CCG GGC GCG GGC GGG CCC TGG GAG ATG CGG GAG CGG 816
Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg
260 265 270

CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA 864
Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu
275 280 285

CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 912
Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr
290 295 300

AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 960
Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu
305 310 315 320

AAC CAT GCC AAT GTT GTA AAG GCC TGT GAT GTT CCT GAA GAA TTG AAT 1008
Asn His Ala Asn Val Val Lys Ala Cys Asp Val Pro Glu Glu Leu Asn
325 330 335

ATT TTG ATT CAT GAT GTG CCT CTT CTA GCA ATG GAA TAC TGT TCT GGA 1056
Ile Leu Ile His Asp Val Pro Leu Leu Ala Met Glu Tyr Cys Ser Gly
340 345 350

GGA GAT CTC CGA AAG CTG CTC AAC AAA CCA GAA AAT TGT TGT GGA CTT 1104
Gly Asp Leu Arg Lys Leu Leu Asn Lys Pro Glu Asn Cys Cys Gly Leu
355 360 365

AAA GAA AGC CAG ATA CTT TCT TTA CTA AGT GAT ATA GGG TCT GGG ATT 1152
Lys Glu Ser Gln Ile Leu Ser Leu Leu Ser Asp Ile Gly Ser Gly Ile
370 375 380

CGA TAT TTG CAT GAA AAC AAA ATT ATA CAT CGA GAT CTA AAA CCT GAA 1200
Arg Tyr Leu His Glu Asn Lys Ile Ile His Arg Asp Leu Lys Pro Glu
385 390 395 400

AAC ATA GTT CTT CAG GAT GTT GGT GGA AAG ATA ATA CAT AAA ATA ATT 1248
Asn Ile Val Leu Gln Asp Val Gly Gly Lys Ile Ile His Lys Ile Ile
405 410 415

GAT CTG GGA TAT GCC AAA GAT GTT GAT CAA GGA AGT CTG TGT ACA TCT 1296
Asp Leu Gly Tyr Ala Lys Asp Val Asp Gln Gly Ser Leu Cys Thr Ser
420 425 430

TTT GTG GGA ACA CTG CAG TAT CTG GCC CCA GAG CTC TTT GAG AAT AAG 1344
Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu Leu Phe Glu Asn Lys
435 440 445

CCT TAC ACA GCC ACT GTT GAT TAT TGG AGC TTT GGG ACC ATG GTA TTT 1392
Pro Tyr Thr Ala Thr Val Asp Tyr Trp Ser Phe Gly Thr Met Val Phe
450 455 460

GAA TGT ATT GCT GGA TAT AGG CCT TTT TTG CAT CAT CTG CAG CCA TTT 1440
Glu Cys Ile Ala Gly Tyr Arg Pro Phe Leu His His Leu Gln Pro Phe
465 470 475 480

ACC TGG CAT GAG AAG ATT AAG AAG AAG GAT CCA AAG TGT ATA TTT GCA 1488
Thr Trp His Glu Lys Ile Lys Lys Lys Asp Pro Lys Cys Ile Phe Ala
485 490 495

TGT GAA GAG ATG TCA GGA GAA GTT CGG TTT AGT AGC CAT TTA CCT CAA 1536
Cys Glu Glu Met Ser Gly Glu Val Arg Phe Ser Ser His Leu Pro Gln
500 505 510

CCA AAT AGC CTT TGT AGT TTA ATA GTA GAA CCC ATG GAA AAC TGG CTA 1584
Pro Asn Ser Leu Cys Ser Leu Ile Val Glu Pro Met Glu Asn Trp Leu
515 520 525

CAG TTG ATG TTG AAT TGG GAC CCT CAG CAG AGA GGA GGA CCT GTT GAC 1632

Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly Gly Pro Val Asp
530 535 540

CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG GAT CAC ATT TTG 1680
Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met Asp His Ile Leu
545 550 555 560

AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT GCA AAG ATA ATT 1728
Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser Ala Lys Ile Ile
565 570 575

TCT TTT CTG TTA CCA CCT GAT GAA AGT CTT CAT TCA CTA CAG TCT CGT 1776
Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser Leu Gln Ser Arg
580 585 590

ATT GAG CGT GAA ACT GGA ATA AAT ACT GGT TCT CAA GAA CTT CTT TCA 1824
Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln Glu Leu Leu Ser
595 600 605

GAG ACA GGA ATT TCT CTG GAT CCT CGG AAA CCA GCC TCT CAA TGT GTT 1872
Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala Ser Gln Cys Val
610 615 620

CTA GAT GGA GTT AGA GGC TGT GAT AGC TAT ATG GTT TAT TTG TTT GAT 1920
Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val Tyr Leu Phe Asp
625 630 635 640

AAA AGT AAA ACT GTA TAT GAA GGG CCA TTT GCT TCC AGA AGT TTA TCT 1968
Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser Arg Ser Leu Ser
645 650 655

GAT TGT GTA AAT TAT ATT GTA CAG GAC AGC AAA ATA CAG CTT CCA ATT 2016
Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile Gln Leu Pro Ile
660 665 670

ATA CAG CTG CGT AAA GTG TGG GCT GAA GCA GTG CAC TAT GTG TCT GGA 2064
Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His Tyr Val Ser Gly
675 680 685

CTA AAA GAA GAC TAT AGC AGG CTC TTT CAG GGA CAA AGG GCA GCA ATG 2112
Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln Arg Ala Ala Met
690 695 700

TTA AGT CTT CTT AGA TAT AAT GCT AAC TTA ACA AAA ATG AAG AAC ACT 2160
Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys Met Lys Asn Thr
705 710 715 720

TTG ATC TCA GCA TCA CAA CAA CTG AAA GCT AAA TTG GAG TTT TTT CAC 2208
Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu Glu Phe Phe His
725 730 735

AAA AGC ATT CAG CTT GAC TTG GAG AGA TAC AGC GAG CAG ATG ACG TAT 2256
Lys Ser Ile Gln Leu Asp Leu Glu Arg Tyr Ser Glu Gln Met Thr Tyr
740 745 750

GGG ATA TCT TCA GAA AAA ATG CTA AAA GCA TGG AAA GAA ATG GAA GAA 2304
Gly Ile Ser Ser Glu Lys Met Leu Lys Ala Trp Lys Glu Met Glu Glu
755 760 765

AAG GCC ATC CAC TAT GCT GAG GTT GGT GTC ATT GGA TAC CTG GAG GAT 2352
Lys Ala Ile His Tyr Ala Glu Val Gly Val Ile Gly Tyr Leu Glu Asp
770 775 780

CAG ATT ATG TCT TTG CAT GCT GAA ATC ATG GGG CTA CAG AAG AGC CCC 2400
Gln Ile Met Ser Leu His Ala Glu Ile Met Gly Leu Gln Lys Ser Pro
785 790 795 800

TAT GGA AGA CGT CAG GGA GAC TTG ATG GAA TCT CTG GAA CAG CGT GCC 2448
Tyr Gly Arg Arg Gln Gly Asp Leu Met Glu Ser Leu Glu Gln Arg Ala
805 810 815

ATT GAT CTA TAT AAG CAG TTA AAA CAC AGA CCT TCA GAT CAC TCC TAC 2496
Ile Asp Leu Tyr Lys Gln Leu Lys His Arg Pro Ser Asp His Ser Tyr
820 825 830

AGT GAC AGC ACA GAG ATG GTG AAA ATC ATT GTG CAC ACT GTG CAG AGT 2544
Ser Asp Ser Thr Glu Met Val Lys Ile Ile Val His Thr Val Gln Ser
835 840 845

CAG GAC CGT GTG CTC AAG GAG CTG TTT GGT CAT TTG AGC AAG TTG TTG 2592
Gln Asp Arg Val Leu Lys Glu Leu Phe Gly His Leu Ser Lys Leu Leu
850 855 860

GGC TGT AAG CAG AAG ATT ATT GAT CTA CTC CCT AAG GTG GAA GTG GCC 2640
Gly Cys Lys Gln Lys Ile Ile Asp Leu Leu Pro Lys Val Glu Val Ala
865 870 875 880

CTC AGT AAT ATC AAA GAA GCT GAC AAT ACT GTC ATG TTC ATG CAG GGA 2688
Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met Phe Met Gln Gly
885 890 895

AAA AGG CAG AAA GAA ATA TGG CAT CTC CTT AAA ATT GCC TGT ACA CAG 2736
Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile Ala Cys Thr Gln
900 905 910

AGT TCT GCC CGC TCT CTT GTA GGA TCC AGT CTA GAA GGT GCA GTA ACC 2784
Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu Gly Ala Val Thr
915 920 925

CCT CAG ACA TCA GCA TGG CTG CCC CCG ACT TCA GCA GAA CAT GAT CAT 2832
Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala Glu His Asp His
930 935 940

TCT CTG TCA TGT GTG GTA ACT CCT CAA GAT GGG GAG ACT TCA GCA CAA 2880
Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu Thr Ser Ala Gln
945 950 955 960

ATG ATA GAA GAA AAT TTG AAC TGC CTT GGC CAT TTA AGC ACT ATT ATT 2928
Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu Ser Thr Ile Ile
965 970 975

CAT GAG GCA AAT GAG GAA CAG GGC AAT AGT ATG ATG AAT CTT GAT TGG 2976
His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met Asn Leu Asp Trp
980 985 990

AGT TGG TTA ACA GAA TGA 2994

Ser Trp Leu Thr Glu
995

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 997 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro
245 250 255
Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg
260 265 270
Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu
275 280 285
Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr
290 295 300
Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu
305 310 315 320
Asn His Ala Asn Val Val Lys Ala Cys Asp Val Pro Glu Glu Leu Asn

325 330 335
Ile Leu Ile His Asp Val Pro Leu Leu Ala Met Glu Tyr Cys Ser Gly
340 345 350
Gly Asp Leu Arg Lys Leu Leu Asn Lys Pro Glu Asn Cys Cys Gly Leu
355 360 365
Lys Glu Ser Gln Ile Leu Ser Leu Leu Ser Asp Ile Gly Ser Gly Ile
370 375 380
Arg Tyr Leu His Glu Asn Lys Ile Ile His Arg Asp Leu Lys Pro Glu
385 390 395 400
Asn Ile Val Leu Gln Asp Val Gly Gly Lys Ile Ile His Lys Ile Ile
405 410 415
Asp Leu Gly Tyr Ala Lys Asp Val Asp Gln Gly Ser Leu Cys Thr Ser
420 425 430
Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu Leu Phe Glu Asn Lys
435 440 445
Pro Tyr Thr Ala Thr Val Asp Tyr Trp Ser Phe Gly Thr Met Val Phe
450 455 460
Glu Cys Ile Ala Gly Tyr Arg Pro Phe Leu His His Leu Gln Pro Phe
465 470 475 480
Thr Trp His Glu Lys Ile Lys Lys Lys Asp Pro Lys Cys Ile Phe Ala
485 490 495
Cys Glu Glu Met Ser Gly Glu Val Arg Phe Ser Ser His Leu Pro Gln
500 505 510
Pro Asn Ser Leu Cys Ser Leu Ile Val Glu Pro Met Glu Asn Trp Leu
515 520 525
Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly Gly Pro Val Asp
530 535 540
Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met Asp His Ile Leu
545 550 555 560
Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser Ala Lys Ile Ile
565 570 575
Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser Leu Gln Ser Arg
580 585 590
Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln Glu Leu Leu Ser
595 600 605
Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala Ser Gln Cys Val
610 615 620
Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val Tyr Leu Phe Asp
625 630 635 640
Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser Arg Ser Leu Ser
645 650 655
Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile Gln Leu Pro Ile
660 665 670
Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His Tyr Val Ser Gly
675 680 685
Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln Arg Ala Ala Met
690 695 700
Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys Met Lys Asn Thr
705 710 715 720
Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu Glu Phe Phe His
725 730 735
Lys Ser Ile Gln Leu Asp Leu Glu Arg Tyr Ser Glu Gln Met Thr Tyr
740 745 750
Gly Ile Ser Ser Glu Lys Met Leu Lys Ala Trp Lys Glu Met Glu Glu
755 760 765
Lys Ala Ile His Tyr Ala Glu Val Gly Val Ile Gly Tyr Leu Glu Asp
770 775 780
Gln Ile Met Ser Leu His Ala Glu Ile Met Gly Leu Gln Lys Ser Pro

785 790 795 800
Tyr Gly Arg Arg Gln Gly Asp Leu Met Glu Ser Leu Glu Gln Arg Ala
805 810 815
Ile Asp Leu Tyr Lys Gln Leu Lys His Arg Pro Ser Asp His Ser Tyr
820 825 830
Ser Asp Ser Thr Glu Met Val Lys Ile Ile Val His Thr Val Gln Ser
835 840 845
Gln Asp Arg Val Leu Lys Glu Leu Phe Gly His Leu Ser Lys Leu Leu
850 855 860
Gly Cys Lys Gln Lys Ile Ile Asp Leu Leu Pro Lys Val Glu Val Ala
865 870 875 880
Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met Phe Met Gln Gly
885 890 895
Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile Ala Cys Thr Gln
900 905 910
Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu Gly Ala Val Thr
915 920 925
Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala Glu His Asp His
930 935 940
Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu Thr Ser Ala Gln
945 950 955 960
Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu Ser Thr Ile Ile
965 970 975
His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met Asn Leu Asp Trp
980 985 990
Ser Trp Leu Thr Glu
995

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2991 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2988
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

ATG GAG CGG CCC CCG GGG CTG CGG CCG GGC GCG GGC GGG CCC TGG GAG 48
Met Glu Arg Pro Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu
1 5 10 15

ATG CGG GAG CGG CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC 96
Met Arg Glu Arg Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr
20 25 30

CAG CAT CGG GAA CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA 144
Gln His Arg Glu Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu
35 40 45

GAG CTA AGT ACC AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT 192

```
Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile
    50                  55                  60

ATG AAG AAG TTG AAC CAT GCC AAT GTT GTA AAG GCC TGT GAT GTT CCT      240
Met Lys Lys Leu Asn His Ala Asn Val Val Lys Ala Cys Asp Val Pro
65                  70                  75                  80

GAA GAA TTG AAT ATT TTG ATT CAT GAT GTG CCT CTT CTA GCA ATG GAA      288
Glu Glu Leu Asn Ile Leu Ile His Asp Val Pro Leu Leu Ala Met Glu
                85                  90                  95

TAC TGT TCT GGA GGA GAT CTC CGA AAG CTG CTC AAC AAA CCA GAA AAT      336
Tyr Cys Ser Gly Gly Asp Leu Arg Lys Leu Leu Asn Lys Pro Glu Asn
            100                 105                 110

TGT TGT GGA CTT AAA GAA AGC CAG ATA CTT TCT TTA CTA AGT GAT ATA      384
Cys Cys Gly Leu Lys Glu Ser Gln Ile Leu Ser Leu Leu Ser Asp Ile
        115                 120                 125

GGG TCT GGG ATT CGA TAT TTG CAT GAA AAC AAA ATT ATA CAT CGA GAT      432
Gly Ser Gly Ile Arg Tyr Leu His Glu Asn Lys Ile Ile His Arg Asp
    130                 135                 140

CTA AAA CCT GAA AAC ATA GTT CTT CAG GAT GTT GGT GGA AAG ATA ATA      480
Leu Lys Pro Glu Asn Ile Val Leu Gln Asp Val Gly Gly Lys Ile Ile
145                 150                 155                 160

CAT AAA ATA ATT GAT CTG GGA TAT GCC AAA GAT GTT GAT CAA GGA AGT      528
His Lys Ile Ile Asp Leu Gly Tyr Ala Lys Asp Val Asp Gln Gly Ser
                165                 170                 175

CTG TGT ACA TCT TTT GTG GGA ACA CTG CAG TAT CTG GCC CCA GAG CTC      576
Leu Cys Thr Ser Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu Leu
            180                 185                 190

TTT GAG AAT AAG CCT TAC ACA GCC ACT GTT GAT TAT TGG AGC TTT GGG      624
Phe Glu Asn Lys Pro Tyr Thr Ala Thr Val Asp Tyr Trp Ser Phe Gly
        195                 200                 205

ACC ATG GTA TTT GAA TGT ATT GCT GGA TAT AGG CCT TTT TTG CAT CAT      672
Thr Met Val Phe Glu Cys Ile Ala Gly Tyr Arg Pro Phe Leu His His
    210                 215                 220

CTG CAG CCA TTT ACC TGG CAT GAG AAG ATT AAG AAG AAG GAT CCA AAG      720
Leu Gln Pro Phe Thr Trp His Glu Lys Ile Lys Lys Lys Asp Pro Lys
225                 230                 235                 240

TGT ATA TTT GCA TGT GAA GAG ATG TCA GGA GAA GTT CGG TTT AGT AGC      768
Cys Ile Phe Ala Cys Glu Glu Met Ser Gly Glu Val Arg Phe Ser Ser
                245                 250                 255

CAT TTA CCT CAA CCA AAT AGC CTT TGT AGT TTA ATA GTA GAA CCC ATG      816
His Leu Pro Gln Pro Asn Ser Leu Cys Ser Leu Ile Val Glu Pro Met
            260                 265                 270

GAA AAC TGG CTA CAG TTG ATG TTG AAT TGG GAC CCT CAG CAG AGA GGA      864
Glu Asn Trp Leu Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly
        275                 280                 285
```

GGA CCT GTT GAC CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG 912
Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met
290 295 300

GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT 960
Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser
305 310 315 320

GCA AAG ATA ATT TCT TTT CTG TTA CCA CCT GAT GAA AGT CTT CAT TCA 1008
Ala Lys Ile Ile Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser
325 330 335

CTA CAG TCT CGT ATT GAG CGT GAA ACT GGA ATA AAT ACT GGT TCT CAA 1056
Leu Gln Ser Arg Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln
340 345 350

GAA CTT CTT TCA GAG ACA GGA ATT TCT CTG GAT CCT CGG AAA CCA GCC 1104
Glu Leu Leu Ser Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala
355 360 365

TCT CAA TGT GTT CTA GAT GGA GTT AGA GGC TGT GAT AGC TAT ATG GTT 1152
Ser Gln Cys Val Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val
370 375 380

TAT TTG TTT GAT AAA AGT AAA ACT GTA TAT GAA GGG CCA TTT GCT TCC 1200
Tyr Leu Phe Asp Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser
385 390 395 400

AGA AGT TTA TCT GAT TGT GTA AAT TAT ATT GTA CAG GAC AGC AAA ATA 1248
Arg Ser Leu Ser Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile
405 410 415

CAG CTT CCA ATT ATA CAG CTG CGT AAA GTG TGG GCT GAA GCA GTG CAC 1296
Gln Leu Pro Ile Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His
420 425 430

TAT GTG TCT GGA CTA AAA GAA GAC TAT AGC AGG CTC TTT CAG GGA CAA 1344
Tyr Val Ser Gly Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln
435 440 445

AGG GCA GCA ATG TTA AGT CTT CTT AGA TAT AAT GCT AAC TTA ACA AAA 1392
Arg Ala Ala Met Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys
450 455 460

ATG AAG AAC ACT TTG ATC TCA GCA TCA CAA CAA CTG AAA GCT AAA TTG 1440
Met Lys Asn Thr Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu
465 470 475 480

GAG TTT TTT CAC AAA AGC ATT CAG CTT GAC TTG GAG AGA TAC AGC GAG 1488
Glu Phe Phe His Lys Ser Ile Gln Leu Asp Leu Glu Arg Tyr Ser Glu
485 490 495

CAG ATG ACG TAT GGG ATA TCT TCA GAA AAA ATG CTA AAA GCA TGG AAA 1536
Gln Met Thr Tyr Gly Ile Ser Ser Glu Lys Met Leu Lys Ala Trp Lys
500 505 510

GAA ATG GAA GAA AAG GCC ATC CAC TAT GCT GAG GTT GGT GTC ATT GGA 1584

Glu Met Glu Glu Lys Ala Ile His Tyr Ala Glu Val Gly Val Ile Gly
515 520 525

TAC CTG GAG GAT CAG ATT ATG TCT TTG CAT GCT GAA ATC ATG GGG CTA 1632
Tyr Leu Glu Asp Gln Ile Met Ser Leu His Ala Glu Ile Met Gly Leu
530 535 540

CAG AAG AGC CCC TAT GGA AGA CGT CAG GGA GAC TTG ATG GAA TCT CTG 1680
Gln Lys Ser Pro Tyr Gly Arg Arg Gln Gly Asp Leu Met Glu Ser Leu
545 550 555 560

GAA CAG CGT GCC ATT GAT CTA TAT AAG CAG TTA AAA CAC AGA CCT TCA 1728
Glu Gln Arg Ala Ile Asp Leu Tyr Lys Gln Leu Lys His Arg Pro Ser
565 570 575

GAT CAC TCC TAC AGT GAC AGC ACA GAG ATG GTG AAA ATC ATT GTG CAC 1776
Asp His Ser Tyr Ser Asp Ser Thr Glu Met Val Lys Ile Ile Val His
580 585 590

ACT GTG CAG AGT CAG GAC CGT GTG CTC AAG GAG CTG TTT GGT CAT TTG 1824
Thr Val Gln Ser Gln Asp Arg Val Leu Lys Glu Leu Phe Gly His Leu
595 600 605

AGC AAG TTG TTG GGC TGT AAG CAG AAG ATT ATT GAT CTA CTC CCT AAG 1872
Ser Lys Leu Leu Gly Cys Lys Gln Lys Ile Ile Asp Leu Leu Pro Lys
610 615 620

GTG GAA GTG GCC CTC AGT AAT ATC AAA GAA GCT GAC AAT ACT GTC ATG 1920
Val Glu Val Ala Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met
625 630 635 640

TTC ATG CAG GGA AAA AGG CAG AAA GAA ATA TGG CAT CTC CTT AAA ATT 1968
Phe Met Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile
645 650 655

GCC TGT ACA CAG AGT TCT GCC CGC TCT CTT GTA GGA TCC AGT CTA GAA 2016
Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu
660 665 670

GGT GCA GTA ACC CCT CAG ACA TCA GCA TGG CTG CCC CCG ACT TCA GCA 2064
Gly Ala Val Thr Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala
675 680 685

GAA CAT GAT CAT TCT CTG TCA TGT GTG GTA ACT CCT CAA GAT GGG GAG 2112
Glu His Asp His Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu
690 695 700

ACT TCA GCA CAA ATG ATA GAA GAA AAT TTG AAC TGC CTT GGC CAT TTA 2160
Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu
705 710 715 720

AGC ACT ATT ATT CAT GAG GCA AAT GAG GAA CAG GGC AAT AGT ATG ATG 2208
Ser Thr Ile Ile His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met
725 730 735

AAT CTT GAT TGG AGT TGG TTA ACA GAA TGG GTA CCG CGG GCC CGG GAT 2256
Asn Leu Asp Trp Ser Trp Leu Thr Glu Trp Val Pro Arg Ala Arg Asp
740 745 750

CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG 2304
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
755 760 765

GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG 2352
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
770 775 780

TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG 2400
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
785 790 795 800

ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC 2448
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
805 810 815

ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC 2496
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
820 825 830

CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA 2544
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
835 840 845

GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC 2592
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
850 855 860

AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC 2640
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
865 870 875 880

ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG 2688
Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
885 890 895

CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC 2736
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
900 905 910

GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC 2784
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
915 920 925

ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC 2832
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
930 935 940

CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC 2880
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
945 950 955 960

ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG 2928
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
965 970 975

GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC 2976

Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
980 985 990

GAG CTG TAC AAG TAA 2991
Glu Leu Tyr Lys
995

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 996 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Met Glu Arg Pro Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu
1 5 10 15
Met Arg Glu Arg Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr
20 25 30
Gln His Arg Glu Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu
35 40 45
Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile
50 55 60
Met Lys Lys Leu Asn His Ala Asn Val Val Lys Ala Cys Asp Val Pro
65 70 75 80
Glu Glu Leu Asn Ile Leu Ile His Asp Val Pro Leu Leu Ala Met Glu
85 90 95
Tyr Cys Ser Gly Gly Asp Leu Arg Lys Leu Leu Asn Lys Pro Glu Asn
100 105 110
Cys Cys Gly Leu Lys Glu Ser Gln Ile Leu Ser Leu Leu Ser Asp Ile
115 120 125
Gly Ser Gly Ile Arg Tyr Leu His Glu Asn Lys Ile Ile His Arg Asp
130 135 140
Leu Lys Pro Glu Asn Ile Val Leu Gln Asp Val Gly Gly Lys Ile Ile
145 150 155 160
His Lys Ile Ile Asp Leu Gly Tyr Ala Lys Asp Val Asp Gln Gly Ser
165 170 175
Leu Cys Thr Ser Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu Leu
180 185 190
Phe Glu Asn Lys Pro Tyr Thr Ala Thr Val Asp Tyr Trp Ser Phe Gly
195 200 205
Thr Met Val Phe Glu Cys Ile Ala Gly Tyr Arg Pro Phe Leu His His
210 215 220
Leu Gln Pro Phe Thr Trp His Glu Lys Ile Lys Lys Lys Asp Pro Lys
225 230 235 240
Cys Ile Phe Ala Cys Glu Glu Met Ser Gly Glu Val Arg Phe Ser Ser
245 250 255
His Leu Pro Gln Pro Asn Ser Leu Cys Ser Leu Ile Val Glu Pro Met
260 265 270
Glu Asn Trp Leu Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly
275 280 285
Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met

290 295 300
Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser
305 310 315 320
Ala Lys Ile Ile Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser
325 330 335
Leu Gln Ser Arg Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln
340 345 350
Glu Leu Leu Ser Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala
355 360 365
Ser Gln Cys Val Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val
370 375 380
Tyr Leu Phe Asp Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser
385 390 395 400
Arg Ser Leu Ser Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile
405 410 415
Gln Leu Pro Ile Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His
420 425 430
Tyr Val Ser Gly Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln
435 440 445
Arg Ala Ala Met Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys
450 455 460
Met Lys Asn Thr Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu
465 470 475 480
Glu Phe Phe His Lys Ser Ile Gln Leu Asp Leu Glu Arg Tyr Ser Glu
485 490 495
Gln Met Thr Tyr Gly Ile Ser Ser Glu Lys Met Leu Lys Ala Trp Lys
500 505 510
Glu Met Glu Glu Lys Ala Ile His Tyr Ala Glu Val Gly Val Ile Gly
515 520 525
Tyr Leu Glu Asp Gln Ile Met Ser Leu His Ala Glu Ile Met Gly Leu
530 535 540
Gln Lys Ser Pro Tyr Gly Arg Arg Gln Gly Asp Leu Met Glu Ser Leu
545 550 555 560
Glu Gln Arg Ala Ile Asp Leu Tyr Lys Gln Leu Lys His Arg Pro Ser
565 570 575
Asp His Ser Tyr Ser Asp Ser Thr Glu Met Val Lys Ile Ile Val His
580 585 590
Thr Val Gln Ser Gln Asp Arg Val Leu Lys Glu Leu Phe Gly His Leu
595 600 605
Ser Lys Leu Leu Gly Cys Lys Gln Lys Ile Ile Asp Leu Leu Pro Lys
610 615 620
Val Glu Val Ala Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met
625 630 635 640
Phe Met Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile
645 650 655
Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu
660 665 670
Gly Ala Val Thr Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala
675 680 685
Glu His Asp His Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu
690 695 700
Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu
705 710 715 720
Ser Thr Ile Ile His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met
725 730 735
Asn Leu Asp Trp Ser Trp Leu Thr Glu Trp Val Pro Arg Ala Arg Asp
740 745 750
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly

```
        755                 760                 765
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
    770                 775                 780
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
785                 790                 795                 800
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
                805                 810                 815
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
            820                 825                 830
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
        835                 840                 845
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
    850                 855                 860
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
865                 870                 875                 880
Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
                885                 890                 895
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
            900                 905                 910
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
        915                 920                 925
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
    930                 935                 940
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
945                 950                 955                 960
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
                965                 970                 975
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
            980                 985                 990
Glu Leu Tyr Lys
        995
```

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1908 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1905
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

```
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG      48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC      96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC     144
```

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCC ATG AGC GAG ACG GTC ATC ATG 768
Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met
245 250 255

AGC GAG ACG GTC ATC TGT TCC AGC CGG GCC ACT GTG ATG CTT TAT GAT 816
Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp
260 265 270

GAT GGC AAC AAG CGA TGG CTC CCT GCT GGC ACG GGT CCC CAG GCC TTC 864
Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe
275 280 285

AGC CGC GTC CAG ATC TAC CAC AAC CCC ACG GCC AAT TCC TTT CGC GTC 912
Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val
290 295 300

GTG GGC CGG AAG ATG CAG CCC GAC CAG CAG GTG GTC ATC AAC TGT GCC 960
Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala
305 310 315 320

ATC GTC CGG GGT GTC AAG TAT AAC CAG GCC ACC CCC AAC TTC CAT CAG 1008
Ile Val Arg Gly Val Lys Tyr Asn Gln Ala Thr Pro Asn Phe His Gln
325 330 335

TGG CGC GAC GCT CGC CAG GTC TGG GGC CTC AAC TTC GGC AGC AAG GAG 1056
Trp Arg Asp Ala Arg Gln Val Trp Gly Leu Asn Phe Gly Ser Lys Glu
340 345 350

GAT GCG GCC CAG TTT GCC GCC GGC ATG GCC AGT GCC CTA GAG GCG TTG 1104
Asp Ala Ala Gln Phe Ala Ala Gly Met Ala Ser Ala Leu Glu Ala Leu
355 360 365

GAA GGA GGT GGG CCC CCT CCA CCC CCA GCA CTT CCC ACC TGG TCG GTC 1152
Glu Gly Gly Gly Pro Pro Pro Pro Pro Ala Leu Pro Thr Trp Ser Val
370 375 380

CCG AAC GGC CCC TCC CCG GAG GAG GTG GAG CAG CAG AAA AGG CAG CAG 1200
Pro Asn Gly Pro Ser Pro Glu Glu Val Glu Gln Gln Lys Arg Gln Gln
385 390 395 400

CCC GGC CCG TCG GAG CAC ATA GAG CGC CGG GTC TCC AAT GCA GGA GGC 1248
Pro Gly Pro Ser Glu His Ile Glu Arg Arg Val Ser Asn Ala Gly Gly
405 410 415

CCA CCT GCT CCC CCC GCT GGG GGT CCA CCC CCA CCA CCA GGA CCT CCC 1296
Pro Pro Ala Pro Pro Ala Gly Gly Pro Pro Pro Pro Pro Gly Pro Pro
420 425 430

CCT CCT CCA GGT CCC CCC CCA CCC CCA GGT TTG CCC CCT TCG GGG GTC 1344
Pro Pro Pro Gly Pro Pro Pro Pro Pro Gly Leu Pro Pro Ser Gly Val
435 440 445

CCA GCT GCA GCG CAC GGA GCA GGG GGA GGA CCA CCC CCT GCA CCC CCT 1392
Pro Ala Ala Ala His Gly Ala Gly Gly Gly Pro Pro Pro Ala Pro Pro
450 455 460

CTC CCG GCA GCA CAG GGC CCT GGT GGT GGG GGA GCT GGG GCC CCA GGC 1440
Leu Pro Ala Ala Gln Gly Pro Gly Gly Gly Gly Ala Gly Ala Pro Gly
465 470 475 480

CTG GCC GCA GCT ATT GCT GGA GCC AAA CTC AGG AAA GTC AGC AAG CAG 1488
Leu Ala Ala Ala Ile Ala Gly Ala Lys Leu Arg Lys Val Ser Lys Gln
485 490 495

GAG GAG GCC TCA GGG GGG CCC ACA GCC CCC AAA GCT GAG AGT GGT CGA 1536

Glu Glu Ala Ser Gly Gly Pro Thr Ala Pro Lys Ala Glu Ser Gly Arg
500 505 510

AGC GGA GGT GGG GGA CTC ATG GAA GAG ATG AAC GCC ATG CTG GCC CGG 1584
Ser Gly Gly Gly Gly Leu Met Glu Glu Met Asn Ala Met Leu Ala Arg
515 520 525

AGA AGG AAA GCC ACG CAA GTT GGG GAG AAA ACC CCC AAG GAT GAA TCT 1632
Arg Arg Lys Ala Thr Gln Val Gly Glu Lys Thr Pro Lys Asp Glu Ser
530 535 540

GCC AAT CAG GAG GAG CCA GAG GCC AGA GTC CCG GCC CAG AGT GAA TCT 1680
Ala Asn Gln Glu Glu Pro Glu Ala Arg Val Pro Ala Gln Ser Glu Ser
545 550 555 560

GTG CGG AGA CCC TGG GAG AAG AAC AGC ACA ACC TTG CCA AGG ATG AAG 1728
Val Arg Arg Pro Trp Glu Lys Asn Ser Thr Thr Leu Pro Arg Met Lys
565 570 575

TCG TCT TCT TCG GTG ACC ACT TCC GAG ACC CAA CCC TGC ACG CCC AGC 1776
Ser Ser Ser Ser Val Thr Thr Ser Glu Thr Gln Pro Cys Thr Pro Ser
580 585 590

TCC AGT GAT TAC TCG GAC CTA CAG AGG GTG AAA CAG GAG CTT CTG GAA 1824
Ser Ser Asp Tyr Ser Asp Leu Gln Arg Val Lys Gln Glu Leu Leu Glu
595 600 605

GAG GTG AAG AAG GAA TTG CAG AAA GTG AAA GAG GAA ATC ATT GAA GCC 1872
Glu Val Lys Lys Glu Leu Gln Lys Val Lys Glu Glu Ile Ile Glu Ala
610 615 620

TTC GTC CAG GAG CTG AGG AAG CGG GGT TCT CCC TGA 1908
Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro
625 630 635

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 635 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys

```
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met
                245                 250                 255
Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp
            260                 265                 270
Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe
        275                 280                 285
Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val
    290                 295                 300
Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala
305                 310                 315                 320
Ile Val Arg Gly Val Lys Tyr Asn Gln Ala Thr Pro Asn Phe His Gln
                325                 330                 335
Trp Arg Asp Ala Arg Gln Val Trp Gly Leu Asn Phe Gly Ser Lys Glu
            340                 345                 350
Asp Ala Ala Gln Phe Ala Ala Gly Met Ala Ser Ala Leu Glu Ala Leu
        355                 360                 365
Glu Gly Gly Gly Pro Pro Pro Pro Pro Ala Leu Pro Thr Trp Ser Val
    370                 375                 380
Pro Asn Gly Pro Ser Pro Glu Glu Val Glu Gln Gln Lys Arg Gln Gln
385                 390                 395                 400
Pro Gly Pro Ser Glu His Ile Glu Arg Arg Val Ser Asn Ala Gly Gly
                405                 410                 415
Pro Pro Ala Pro Pro Ala Gly Gly Pro Pro Pro Pro Pro Gly Pro Pro
            420                 425                 430
Pro Pro Pro Gly Pro Pro Pro Pro Pro Gly Leu Pro Pro Ser Gly Val
        435                 440                 445
Pro Ala Ala Ala His Gly Ala Gly Gly Gly Pro Pro Pro Ala Pro Pro
    450                 455                 460
Leu Pro Ala Ala Gln Gly Pro Gly Gly Gly Gly Ala Gly Ala Pro Gly
465                 470                 475                 480
Leu Ala Ala Ala Ile Ala Gly Ala Lys Leu Arg Lys Val Ser Lys Gln
                485                 490                 495
Glu Glu Ala Ser Gly Gly Pro Thr Ala Pro Lys Ala Glu Ser Gly Arg
            500                 505                 510
Ser Gly Gly Gly Gly Leu Met Glu Glu Met Asn Ala Met Leu Ala Arg
        515                 520                 525
Arg Arg Lys Ala Thr Gln Val Gly Glu Lys Thr Pro Lys Asp Glu Ser
```

530 535 540
Ala Asn Gln Glu Glu Pro Glu Ala Arg Val Pro Ala Gln Ser Glu Ser
545 550 555 560
Val Arg Arg Pro Trp Glu Lys Asn Ser Thr Thr Leu Pro Arg Met Lys
565 570 575
Ser Ser Ser Ser Val Thr Thr Ser Glu Thr Gln Pro Cys Thr Pro Ser
580 585 590
Ser Ser Asp Tyr Ser Asp Leu Gln Arg Val Lys Gln Glu Leu Leu Glu
595 600 605
Glu Val Lys Lys Glu Leu Gln Lys Val Lys Glu Glu Ile Ile Glu Ala
610 615 620
Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro
625 630 635

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1329 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1326
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 384
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 432
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 480
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 528
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 576
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 624
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 672
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 720
225 230 235 240

GGA CTC AGA TCT CGA GCT CAA GCT TCA ATG GCT GCC ATC CGG AAG AAA
Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys 768
245 250 255

CTG GTG ATT GTT GGT GAT GGA GCC TGT GGA AAG ACA TGC TTG CTC ATA
Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 816
260 265 270

GTC TTC AGC AAG GAC CAG TTC CCA GAG GTG TAT GTG CCC ACA GTG TTT
Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe 864
275 280 285

GAG AAC TAT GTG GCA GAT ATC GAG GTG GAT GGA AAG CAG GTA GAG TTG
Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu 912
290 295 300

GCT TTG TGG GAC ACA GCT GGG CAG GAA GAT TAT GAT CGC CTG AGG CCC
Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro 960
305 310 315 320

CTC TCC TAC CCA GAT ACC GAT GTT ATA CTG ATG TGT TTT TCC ATC GAC
Leu Ser Tyr Pro Asp Thr Asp Val Ile Leu Met Cys Phe Ser Ile Asp 1008
325 330 335

AGC CCT GAT AGT TTA GAA AAC ATC CCA GAA AAG TGG ACC CCA GAA GTC 1056

Ser Pro Asp Ser Leu Glu Asn Ile Pro Glu Lys Trp Thr Pro Glu Val
340 345 350

AAG CAT TTC TGT CCC AAC GTG CCC ATC ATC CTG GTT GGG AAT AAG AAG 1104
Lys His Phe Cys Pro Asn Val Pro Ile Ile Leu Val Gly Asn Lys Lys
355 360 365

GAT CTT CGG AAT GAT GAG CAC ACA AGG CGG GAG CTA GCC AAG ATG AAG 1152
Asp Leu Arg Asn Asp Glu His Thr Arg Arg Glu Leu Ala Lys Met Lys
370 375 380

CAG GAG CCG GTG AAA CCT GAA GAA GGC AGA GAT ATG GCA AAC AGG ATT 1200
Gln Glu Pro Val Lys Pro Glu Glu Gly Arg Asp Met Ala Asn Arg Ile
385 390 395 400

GGC GCT TTT GGG TAC ATG GAG TGT TCA GCA AAG ACC AAA GAT GGA GTG 1248
Gly Ala Phe Gly Tyr Met Glu Cys Ser Ala Lys Thr Lys Asp Gly Val
405 410 415

AGA GAG GTT TTT GAA ATG GCT ACG AGA GCT GCT CTG CAA GCT AGA CGT 1296
Arg Glu Val Phe Glu Met Ala Thr Arg Ala Ala Leu Gln Ala Arg Arg
420 425 430

GGG AAG AAA AAA TCT GGT TGC CTT GTC TTG TGA 1329
Gly Lys Lys Lys Ser Gly Cys Leu Val Leu
435 440

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 442 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys
245 250 255
Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile
260 265 270
Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe
275 280 285
Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu
290 295 300
Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro
305 310 315 320
Leu Ser Tyr Pro Asp Thr Asp Val Ile Leu Met Cys Phe Ser Ile Asp
325 330 335
Ser Pro Asp Ser Leu Glu Asn Ile Pro Glu Lys Trp Thr Pro Glu Val
340 345 350
Lys His Phe Cys Pro Asn Val Pro Ile Ile Leu Val Gly Asn Lys Lys
355 360 365
Asp Leu Arg Asn Asp Glu His Thr Arg Arg Glu Leu Ala Lys Met Lys
370 375 380
Gln Glu Pro Val Lys Pro Glu Glu Gly Arg Asp Met Ala Asn Arg Ile
385 390 395 400
Gly Ala Phe Gly Tyr Met Glu Cys Ser Ala Lys Thr Lys Asp Gly Val
405 410 415
Arg Glu Val Phe Glu Met Ala Thr Arg Ala Ala Leu Gln Ala Arg Arg
420 425 430
Gly Lys Lys Lys Ser Gly Cys Leu Val Leu
435 440

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1140 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1137
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

ATG GAC CAT TAT GAT TCT CAG CAA ACC AAC GAT TAC ATG CAG CCA GAA 48

Met Asp His Tyr Asp Ser Gln Gln Thr Asn Asp Tyr Met Gln Pro Glu
1 5 10 15

GAG GAC TGG GAC CGG GAC CTG CTC CTG GAC CCG GCC TGG GAG AAG CAG 96
Glu Asp Trp Asp Arg Asp Leu Leu Leu Asp Pro Ala Trp Glu Lys Gln
20 25 30

CAG AGA AAG ACA TTC ACG GCA TGG TGT AAC TCC CAC CTC CGG AAG GCG 144
Gln Arg Lys Thr Phe Thr Ala Trp Cys Asn Ser His Leu Arg Lys Ala
35 40 45

GGG ACA CAG ATC GAG AAC ATC GAA GAG GAC TTC CGG GAT GGC CTG AAG 192
Gly Thr Gln Ile Glu Asn Ile Glu Glu Asp Phe Arg Asp Gly Leu Lys
50 55 60

CTC ATG CTG CTG CTG GAG GTC ATC TCA GGT GAA CGC TTG GCC AAG CCA 240
Leu Met Leu Leu Leu Glu Val Ile Ser Gly Glu Arg Leu Ala Lys Pro
65 70 75 80

GAG CGA GGC AAG ATG AGA GTG CAC AAG ATC TCC AAC GTC AAC AAG GCC 288
Glu Arg Gly Lys Met Arg Val His Lys Ile Ser Asn Val Asn Lys Ala
85 90 95

CTG GAT TTC ATA GCC AGC AAA GGC GTC AAA CTG GTG TCC ATC GGA GCC 336
Leu Asp Phe Ile Ala Ser Lys Gly Val Lys Leu Val Ser Ile Gly Ala
100 105 110

GAA GAA ATC GTG GAT GGG AAT GTG AAG ATG ACC CTG GGC ATG ATC TGG 384
Glu Glu Ile Val Asp Gly Asn Val Lys Met Thr Leu Gly Met Ile Trp
115 120 125

ACC ATC ATC CTG CGC AGG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG 432
Thr Ile Ile Leu Arg Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys
130 135 140

GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC 480
Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp
145 150 155 160

GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC 528
Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly
165 170 175

GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC 576
Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly
180 185 190

AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC 624
Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly
195 200 205

GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC 672
Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe
210 215 220

TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC 720
Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe
225 230 235 240

TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG 768
Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu
245 250 255

GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG 816
Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys
260 265 270

GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC 864
Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser
275 280 285

CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG 912
His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val
290 295 300

AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC 960
Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala
305 310 315 320

GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG 1008
Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu
325 330 335

CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC 1056
Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro
340 345 350

AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC 1104
Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala
355 360 365

GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 1140
Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
370 375

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 379 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Met Asp His Tyr Asp Ser Gln Gln Thr Asn Asp Tyr Met Gln Pro Glu
1 5 10 15
Glu Asp Trp Asp Arg Asp Leu Leu Leu Asp Pro Ala Trp Glu Lys Gln
20 25 30
Gln Arg Lys Thr Phe Thr Ala Trp Cys Asn Ser His Leu Arg Lys Ala
35 40 45
Gly Thr Gln Ile Glu Asn Ile Glu Glu Asp Phe Arg Asp Gly Leu Lys

```
    50                  55                  60
Leu Met Leu Leu Leu Glu Val Ile Ser Gly Glu Arg Leu Ala Lys Pro
65                  70                  75                  80
Glu Arg Gly Lys Met Arg Val His Lys Ile Ser Asn Val Asn Lys Ala
                85                  90                  95
Leu Asp Phe Ile Ala Ser Lys Gly Val Lys Leu Val Ser Ile Gly Ala
            100                 105                 110
Glu Glu Ile Val Asp Gly Asn Val Lys Met Thr Leu Gly Met Ile Trp
        115                 120                 125
Thr Ile Ile Leu Arg Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys
    130                 135                 140
Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp
145                 150                 155                 160
Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly
                165                 170                 175
Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly
            180                 185                 190
Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly
        195                 200                 205
Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe
    210                 215                 220
Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe
225                 230                 235                 240
Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu
                245                 250                 255
Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys
            260                 265                 270
Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser
        275                 280                 285
His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val
    290                 295                 300
Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala
305                 310                 315                 320
Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu
                325                 330                 335
Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro
            340                 345                 350
Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala
        355                 360                 365
Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 3516 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

  (A) NAME/KEY: Coding Sequence
  (B) LOCATION: 1...3513
  (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GCC ATG AAC GCC CCC GAG CGG CAG CCC CAA CCC 768
Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro
245 250 255

GAC GGC GGG GAC GCC CCA GGC CAC GAG CCT GGG GGC AGC CCC CAA GAC 816
Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp
260 265 270

GAG CTT GAC TTC TCC ATC CTC TTC GAC TAT GAG TAT TTG AAT CCG AAC 864
Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn
275 280 285

GAA GAA GAG CCG AAT GCA CAT AAG GTC GCC AGC CCA CCC TCC GGA CCC 912
Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro
290 295 300

GCA TAC CCC GAT GAT GTA ATG GAC TAT GGC CTC AAG CCA TAC AGC CCC 960
Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro
305 310 315 320

CTT GCT AGT CTC TCT GGC GAG CCC CCC GGC CGA TTC GGA GAG CCG GAT 1008
Leu Ala Ser Leu Ser Gly Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp
325 330 335

AGG GTA GGG CCG CAG AAG TTT CTG AGC GCG GCC AAG CCA GCA GGG GCC 1056
Arg Val Gly Pro Gln Lys Phe Leu Ser Ala Ala Lys Pro Ala Gly Ala
340 345 350

TCG GGC CTG AGC CCT CGG ATC GAG ATC ACT CCG TCC CAC GAA CTG ATC 1104
Ser Gly Leu Ser Pro Arg Ile Glu Ile Thr Pro Ser His Glu Leu Ile
355 360 365

CAG GCA GTG GGG CCC CTC CGC ATG AGA GAC GCG GGC CTC CTG GTG GAG 1152
Gln Ala Val Gly Pro Leu Arg Met Arg Asp Ala Gly Leu Leu Val Glu
370 375 380

CAG CCT CCC CTG GCC GGG GTG GCC GCC AGC CCG AGG TTC ACC CTG CCC 1200
Gln Pro Pro Leu Ala Gly Val Ala Ala Ser Pro Arg Phe Thr Leu Pro
385 390 395 400

GTG CCC GGC TTC GAG GGC TAC CGC GAG CCG CTT TGC TTG AGC CCC GCT 1248
Val Pro Gly Phe Glu Gly Tyr Arg Glu Pro Leu Cys Leu Ser Pro Ala
405 410 415

AGC AGC GGC TCC TCT GCC AGC TTC ATT TCT GAC ACC TTC TCC CCC TAC 1296
Ser Ser Gly Ser Ser Ala Ser Phe Ile Ser Asp Thr Phe Ser Pro Tyr
420 425 430

ACC TCG CCC TGC GTC TCG CCC AAT AAC GGC GGG CCC GAC GAC CTG TGT 1344
Thr Ser Pro Cys Val Ser Pro Asn Asn Gly Gly Pro Asp Asp Leu Cys
435 440 445

CCG CAG TTT CAA AAC ATC CCT GCT CAT TAT TCC CCC AGA ACC TCG CCA 1392
Pro Gln Phe Gln Asn Ile Pro Ala His Tyr Ser Pro Arg Thr Ser Pro
450 455 460

ATA ATG TCA CCT CGA ACC AGC CTC GCC GAG GAC AGC TGC CTG GGC CGC 1440
Ile Met Ser Pro Arg Thr Ser Leu Ala Glu Asp Ser Cys Leu Gly Arg
465 470 475 480

CAC TCG CCC GTG CCC CGT CCG GCC TCC CGC TCC TCA TCG CCT GGT GCC 1488
His Ser Pro Val Pro Arg Pro Ala Ser Arg Ser Ser Ser Pro Gly Ala
485 490 495

AAG CGG AGG CAT TCG TGC GCC GAG GCC TTG GTT GCC CTG CCG CCC GGA 1536
Lys Arg Arg His Ser Cys Ala Glu Ala Leu Val Ala Leu Pro Pro Gly
500 505 510

GCC TCA CCC CAG CGC TCC CGG AGC CCC TCG CCG CAG CCC TCA TCT CAC 1584
Ala Ser Pro Gln Arg Ser Arg Ser Pro Ser Pro Gln Pro Ser Ser His
515 520 525

GTG GCA CCC CAG GAC CAC GGC TCC CCG GCT GGG TAC CCC CCT GTG GCT 1632
Val Ala Pro Gln Asp His Gly Ser Pro Ala Gly Tyr Pro Pro Val Ala
530 535 540

GGC TCT GCC GTG ATC ATG GAT GCC CTG AAC AGC CTC GCC ACG GAC TCG 1680
Gly Ser Ala Val Ile Met Asp Ala Leu Asn Ser Leu Ala Thr Asp Ser
545 550 555 560

CCT TGT GGG ATC CCC CCC AAG ATG TGG AAG ACC AGC CCT GAC CCC TCG 1728
Pro Cys Gly Ile Pro Pro Lys Met Trp Lys Thr Ser Pro Asp Pro Ser
565 570 575

CCG GTG TCT GCC GCC CCA TCC AAG GCC GGC CTG CCT CGC CAC ATC TAC 1776
Pro Val Ser Ala Ala Pro Ser Lys Ala Gly Leu Pro Arg His Ile Tyr
580 585 590

CCG GCC GTG GAG TTC CTG GGG CCC TGC GAG CAG GGC GAG AGG AGA AAC 1824
Pro Ala Val Glu Phe Leu Gly Pro Cys Glu Gln Gly Glu Arg Arg Asn
595 600 605

TCG GCT CCA GAA TCC ATC CTG CTG GTT CCG CCC ACT TGG CCC AAG CCG 1872
Ser Ala Pro Glu Ser Ile Leu Leu Val Pro Pro Thr Trp Pro Lys Pro
610 615 620

CTG GTG CCT GCC ATT CCC ATC TGC AGC ATC CCA GTG ACT GCA TCC CTC 1920
Leu Val Pro Ala Ile Pro Ile Cys Ser Ile Pro Val Thr Ala Ser Leu
625 630 635 640

CCT CCA CTT GAG TGG CCG CTG TCC AGT CAG TCA GGC TCT TAC GAG CTG 1968
Pro Pro Leu Glu Trp Pro Leu Ser Ser Gln Ser Gly Ser Tyr Glu Leu
645 650 655

CGG ATC GAG GTG CAG CCC AAG CCA CAT CAC CGG GCC CAC TAT GAG ACA 2016
Arg Ile Glu Val Gln Pro Lys Pro His His Arg Ala His Tyr Glu Thr
660 665 670

GAA GGC AGC CGA GGG GCT GTC AAA GCT CCA ACT GGA GGC CAC CCT GTG 2064
Glu Gly Ser Arg Gly Ala Val Lys Ala Pro Thr Gly Gly His Pro Val
675 680 685

GTT CAG CTC CAT GGC TAC ATG GAA AAC AAG CCT CTG GGA CTT CAG ATC 2112

Val Gln Leu His Gly Tyr Met Glu Asn Lys Pro Leu Gly Leu Gln Ile
690 695 700

TTC ATT GGG ACA GCT GAT GAG CGG ATC CTT AAG CCG CAC GCC TTC TAC 2160
Phe Ile Gly Thr Ala Asp Glu Arg Ile Leu Lys Pro His Ala Phe Tyr
705 710 715 720

CAG GTG CAC CGA ATC ACG GGG AAA ACT GTC ACC ACC ACC AGC TAT GAG 2208
Gln Val His Arg Ile Thr Gly Lys Thr Val Thr Thr Thr Ser Tyr Glu
725 730 735

AAG ATA GTG GGC AAC ACC AAA GTC CTG GAG ATC CCC TTG GAG CCC AAA 2256
Lys Ile Val Gly Asn Thr Lys Val Leu Glu Ile Pro Leu Glu Pro Lys
740 745 750

AAC AAC ATG AGG GCA ACC ATC GAC TGT GCG GGG ATC TTG AAG CTT AGA 2304
Asn Asn Met Arg Ala Thr Ile Asp Cys Ala Gly Ile Leu Lys Leu Arg
755 760 765

AAC GCC GAC ATT GAG CTG CGG AAA GGC GAG ACG GAC ATT GGA AGA AAG 2352
Asn Ala Asp Ile Glu Leu Arg Lys Gly Glu Thr Asp Ile Gly Arg Lys
770 775 780

AAC ACG CGG GTG AGA CTG GTT TTC CGA GTT CAC ATC CCA GAG TCC AGT 2400
Asn Thr Arg Val Arg Leu Val Phe Arg Val His Ile Pro Glu Ser Ser
785 790 795 800

GGC AGA ATC GTC TCT TTA CAG ACT GCA TCT AAC CCC ATC GAG TGC TCC 2448
Gly Arg Ile Val Ser Leu Gln Thr Ala Ser Asn Pro Ile Glu Cys Ser
805 810 815

CAG CGA TCT GCT CAC GAG CTG CCC ATG GTT GAA AGA CAA GAC ACA GAC 2496
Gln Arg Ser Ala His Glu Leu Pro Met Val Glu Arg Gln Asp Thr Asp
820 825 830

AGC TGC CTG GTC TAT GGC GGC CAG CAA ATG ATC CTC ACG GGG CAG AAC 2544
Ser Cys Leu Val Tyr Gly Gly Gln Gln Met Ile Leu Thr Gly Gln Asn
835 840 845

TTT ACA TCC GAG TCC AAA GTT GTG TTT ACT GAG AAG ACC ACA GAT GGA 2592
Phe Thr Ser Glu Ser Lys Val Val Phe Thr Glu Lys Thr Thr Asp Gly
850 855 860

CAG CAA ATT TGG GAG ATG GAA GCC ACG GTG GAT AAG GAC AAG AGC CAG 2640
Gln Gln Ile Trp Glu Met Glu Ala Thr Val Asp Lys Asp Lys Ser Gln
865 870 875 880

CCC AAC ATG CTT TTT GTT GAG ATC CCT GAA TAT CGG AAC AAG CAT ATC 2688
Pro Asn Met Leu Phe Val Glu Ile Pro Glu Tyr Arg Asn Lys His Ile
885 890 895

CGC ACA CCT GTA AAA GTG AAC TTC TAC GTC ATC AAT GGG AAG AGA AAA 2736
Arg Thr Pro Val Lys Val Asn Phe Tyr Val Ile Asn Gly Lys Arg Lys
900 905 910

CGA AGT CAG CCT CAG CAC TTT ACC TAC CAC CCA GTC CCA GCC ATC AAG 2784
Arg Ser Gln Pro Gln His Phe Thr Tyr His Pro Val Pro Ala Ile Lys
915 920 925

ACG GAG CCC ACG GAT GAA TAT GAC CCC ACT CTG ATC TGC AGC CCC ACC 2832
Thr Glu Pro Thr Asp Glu Tyr Asp Pro Thr Leu Ile Cys Ser Pro Thr
930 935 940

CAT GGA GGC CTG GGG AGC CAG CCT TAC TAC CCC CAG CAC CCG ATG GTG 2880
His Gly Gly Leu Gly Ser Gln Pro Tyr Tyr Pro Gln His Pro Met Val
945 950 955 960

GCC GAG TCC CCC TCC TGC CTC GTG GCC ACC ATG GCT CCC TGC CAG CAG 2928
Ala Glu Ser Pro Ser Cys Leu Val Ala Thr Met Ala Pro Cys Gln Gln
965 970 975

TTC CGC ACG GGG CTC TCA TCC CCT GAC GCC CGC TAC CAG CAA CAG AAC 2976
Phe Arg Thr Gly Leu Ser Ser Pro Asp Ala Arg Tyr Gln Gln Gln Asn
980 985 990

CCA GCG GCC GTA CTC TAC CAG CGG AGC AAG AGC CTG AGC CCC AGC CTG 3024
Pro Ala Ala Val Leu Tyr Gln Arg Ser Lys Ser Leu Ser Pro Ser Leu
995 1000 1005

CTG GGC TAT CAG CAG CCG GCC CTC ATG GCC GCC CCG CTG TCC CTT GCG 3072
Leu Gly Tyr Gln Gln Pro Ala Leu Met Ala Ala Pro Leu Ser Leu Ala
1010 1015 1020

GAC GCT CAC CGC TCT GTG CTG GTG CAC GCC GGC TCC CAG GGC CAG AGC 3120
Asp Ala His Arg Ser Val Leu Val His Ala Gly Ser Gln Gly Gln Ser
1025 1030 1035 1040

TCA GCC CTG CTC CAC CCC TCT CCG ACC AAC CAG CAG GCC TCG CCT GTG 3168
Ser Ala Leu Leu His Pro Ser Pro Thr Asn Gln Gln Ala Ser Pro Val
1045 1050 1055

ATC CAC TAC TCA CCC ACC AAC CAG CAG CTG CGC TGC GGA AGC CAC CAG 3216
Ile His Tyr Ser Pro Thr Asn Gln Gln Leu Arg Cys Gly Ser His Gln
1060 1065 1070

GAG TTC CAG CAC ATC ATG TAC TGC GAG AAT TTC GCA CCA GGC ACC ACC 3264
Glu Phe Gln His Ile Met Tyr Cys Glu Asn Phe Ala Pro Gly Thr Thr
1075 1080 1085

AGA CCT GGC CCG CCC CCG GTC AGT CAA GGT CAG AGG CTG AGC CCG GGT 3312
Arg Pro Gly Pro Pro Pro Val Ser Gln Gly Gln Arg Leu Ser Pro Gly
1090 1095 1100

TCC TAC CCC ACA GTC ATT CAG CAG CAG AAT GCC ACG AGC CAA AGA GCC 3360
Ser Tyr Pro Thr Val Ile Gln Gln Gln Asn Ala Thr Ser Gln Arg Ala
1105 1110 1115 1120

GCC AAA AAC GGA CCC CCG GTC AGT GAC CAA AAG GAA GTA TTA CCT GCG 3408
Ala Lys Asn Gly Pro Pro Val Ser Asp Gln Lys Glu Val Leu Pro Ala
1125 1130 1135

GGG GTG ACC ATT AAA CAG GAG CAG AAC TTG GAC CAG ACC TAC TTG GAT 3456
Gly Val Thr Ile Lys Gln Glu Gln Asn Leu Asp Gln Thr Tyr Leu Asp
1140 1145 1150

GAT GTT AAT GAA ATT ATC AGG AAG GAG TTT TCA GGA CCT CCT GCC AGA 3504

Asp Val Asn Glu Ile Ile Arg Lys Glu Phe Ser Gly Pro Pro Ala Arg
1155 1160 1165

AAT CAG ACG TAA 3516
Asn Gln Thr
1170

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro
245 250 255
Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp
260 265 270
Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn
275 280 285
Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro

290 295 300
Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro
305 310 315 320
Leu Ala Ser Leu Ser Gly Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp
325 330 335
Arg Val Gly Pro Gln Lys Phe Leu Ser Ala Ala Lys Pro Ala Gly Ala
340 345 350
Ser Gly Leu Ser Pro Arg Ile Glu Ile Thr Pro Ser His Glu Leu Ile
355 360 365
Gln Ala Val Gly Pro Leu Arg Met Arg Asp Ala Gly Leu Leu Val Glu
370 375 380
Gln Pro Pro Leu Ala Gly Val Ala Ala Ser Pro Arg Phe Thr Leu Pro
385 390 395 400
Val Pro Gly Phe Glu Gly Tyr Arg Glu Pro Leu Cys Leu Ser Pro Ala
405 410 415
Ser Ser Gly Ser Ser Ala Ser Phe Ile Ser Asp Thr Phe Ser Pro Tyr
420 425 430
Thr Ser Pro Cys Val Ser Pro Asn Asn Gly Gly Pro Asp Asp Leu Cys
435 440 445
Pro Gln Phe Gln Asn Ile Pro Ala His Tyr Ser Pro Arg Thr Ser Pro
450 455 460
Ile Met Ser Pro Arg Thr Ser Leu Ala Glu Asp Ser Cys Leu Gly Arg
465 470 475 480
His Ser Pro Val Pro Arg Pro Ala Ser Arg Ser Ser Ser Pro Gly Ala
485 490 495
Lys Arg Arg His Ser Cys Ala Glu Ala Leu Val Ala Leu Pro Pro Gly
500 505 510
Ala Ser Pro Gln Arg Ser Arg Ser Pro Ser Pro Gln Pro Ser Ser His
515 520 525
Val Ala Pro Gln Asp His Gly Ser Pro Ala Gly Tyr Pro Pro Val Ala
530 535 540
Gly Ser Ala Val Ile Met Asp Ala Leu Asn Ser Leu Ala Thr Asp Ser
545 550 555 560
Pro Cys Gly Ile Pro Pro Lys Met Trp Lys Thr Ser Pro Asp Pro Ser
565 570 575
Pro Val Ser Ala Ala Pro Ser Lys Ala Gly Leu Pro Arg His Ile Tyr
580 585 590
Pro Ala Val Glu Phe Leu Gly Pro Cys Glu Gln Gly Glu Arg Arg Asn
595 600 605
Ser Ala Pro Glu Ser Ile Leu Leu Val Pro Pro Thr Trp Pro Lys Pro
610 615 620
Leu Val Pro Ala Ile Pro Ile Cys Ser Ile Pro Val Thr Ala Ser Leu
625 630 635 640
Pro Pro Leu Glu Trp Pro Leu Ser Ser Gln Ser Gly Ser Tyr Glu Leu
645 650 655
Arg Ile Glu Val Gln Pro Lys Pro His His Arg Ala His Tyr Glu Thr
660 665 670
Glu Gly Ser Arg Gly Ala Val Lys Ala Pro Thr Gly Gly His Pro Val
675 680 685
Val Gln Leu His Gly Tyr Met Glu Asn Lys Pro Leu Gly Leu Gln Ile
690 695 700
Phe Ile Gly Thr Ala Asp Glu Arg Ile Leu Lys Pro His Ala Phe Tyr
705 710 715 720
Gln Val His Arg Ile Thr Gly Lys Thr Val Thr Thr Thr Ser Tyr Glu
725 730 735
Lys Ile Val Gly Asn Thr Lys Val Leu Glu Ile Pro Leu Glu Pro Lys
740 745 750
Asn Asn Met Arg Ala Thr Ile Asp Cys Ala Gly Ile Leu Lys Leu Arg

755 760 765
Asn Ala Asp Ile Glu Leu Arg Lys Gly Glu Thr Asp Ile Gly Arg Lys
770 775 780
Asn Thr Arg Val Arg Leu Val Phe Arg Val His Ile Pro Glu Ser Ser
785 790 795 800
Gly Arg Ile Val Ser Leu Gln Thr Ala Ser Asn Pro Ile Glu Cys Ser
805 810 815
Gln Arg Ser Ala His Glu Leu Pro Met Val Glu Arg Gln Asp Thr Asp
820 825 830
Ser Cys Leu Val Tyr Gly Gly Gln Gln Met Ile Leu Thr Gly Gln Asn
835 840 845
Phe Thr Ser Glu Ser Lys Val Val Phe Thr Glu Lys Thr Thr Asp Gly
850 855 860
Gln Gln Ile Trp Glu Met Glu Ala Thr Val Asp Lys Asp Lys Ser Gln
865 870 875 880
Pro Asn Met Leu Phe Val Glu Ile Pro Glu Tyr Arg Asn Lys His Ile
885 890 895
Arg Thr Pro Val Lys Val Asn Phe Tyr Val Ile Asn Gly Lys Arg Lys
900 905 910
Arg Ser Gln Pro Gln His Phe Thr Tyr His Pro Val Pro Ala Ile Lys
915 920 925
Thr Glu Pro Thr Asp Glu Tyr Asp Pro Thr Leu Ile Cys Ser Pro Thr
930 935 940
His Gly Gly Leu Gly Ser Gln Pro Tyr Tyr Pro Gln His Pro Met Val
945 950 955 960
Ala Glu Ser Pro Ser Cys Leu Val Ala Thr Met Ala Pro Cys Gln Gln
965 970 975
Phe Arg Thr Gly Leu Ser Ser Pro Asp Ala Arg Tyr Gln Gln Gln Asn
980 985 990
Pro Ala Ala Val Leu Tyr Gln Arg Ser Lys Ser Leu Ser Pro Ser Leu
995 1000 1005
Leu Gly Tyr Gln Gln Pro Ala Leu Met Ala Ala Pro Leu Ser Leu Ala
1010 1015 1020
Asp Ala His Arg Ser Val Leu Val His Ala Gly Ser Gln Gly Gln Ser
025 1030 1035 1040
Ser Ala Leu Leu His Pro Ser Pro Thr Asn Gln Gln Ala Ser Pro Val
1045 1050 1055
Ile His Tyr Ser Pro Thr Asn Gln Gln Leu Arg Cys Gly Ser His Gln
1060 1065 1070
Glu Phe Gln His Ile Met Tyr Cys Glu Asn Phe Ala Pro Gly Thr Thr
1075 1080 1085
Arg Pro Gly Pro Pro Pro Val Ser Gln Gly Gln Arg Leu Ser Pro Gly
1090 1095 1100
Ser Tyr Pro Thr Val Ile Gln Gln Gln Asn Ala Thr Ser Gln Arg Ala
105 1110 1115 1120
Ala Lys Asn Gly Pro Pro Val Ser Asp Gln Lys Glu Val Leu Pro Ala
1125 1130 1135
Gly Val Thr Ile Lys Gln Glu Gln Asn Leu Asp Gln Thr Tyr Leu Asp
1140 1145 1150
Asp Val Asn Glu Ile Ile Arg Lys Glu Phe Ser Gly Pro Pro Ala Arg
1155 1160 1165
Asn Gln Thr
1170

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3546 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3543
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

```
ATG AAC GCC CCC GAG CGG CAG CCC CAA CCC GAC GGC GGG GAC GCC CCA      48
Met Asn Ala Pro Glu Arg Gln Pro Gln Pro Asp Gly Gly Asp Ala Pro
 1               5                  10                  15

GGC CAC GAG CCT GGG GGC AGC CCC CAA GAC GAG CTT GAC TTC TCC ATC      96
Gly His Glu Pro Gly Gly Ser Pro Gln Asp Glu Leu Asp Phe Ser Ile
            20                  25                  30

CTC TTC GAC TAT GAG TAT TTG AAT CCG AAC GAA GAA GAG CCG AAT GCA     144
Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn Glu Glu Glu Pro Asn Ala
        35                  40                  45

CAT AAG GTC GCC AGC CCA CCC TCC GGA CCC GCA TAC CCC GAT GAT GTA     192
His Lys Val Ala Ser Pro Pro Ser Gly Pro Ala Tyr Pro Asp Asp Val
    50                  55                  60

ATG GAC TAT GGC CTC AAG CCA TAC AGC CCC CTT GCT AGT CTC TCT GGC     240
Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro Leu Ala Ser Leu Ser Gly
65                  70                  75                  80

GAG CCC CCC GGC CGA TTC GGA GAG CCG GAT AGG GTA GGG CCG CAG AAG     288
Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp Arg Val Gly Pro Gln Lys
                85                  90                  95

TTT CTG AGC GCG GCC AAG CCA GCA GGG GCC TCG GGC CTG AGC CCT CGG     336
Phe Leu Ser Ala Ala Lys Pro Ala Gly Ala Ser Gly Leu Ser Pro Arg
            100                 105                 110

ATC GAG ATC ACT CCG TCC CAC GAA CTG ATC CAG GCA GTG GGG CCC CTC     384
Ile Glu Ile Thr Pro Ser His Glu Leu Ile Gln Ala Val Gly Pro Leu
        115                 120                 125

CGC ATG AGA GAC GCG GGC CTC CTG GTG GAG CAG CCT CCC CTG GCC GGG     432
Arg Met Arg Asp Ala Gly Leu Leu Val Glu Gln Pro Pro Leu Ala Gly
    130                 135                 140

GTG GCC GCC AGC CCG AGG TTC ACC CTG CCC GTG CCC GGC TTC GAG GGC     480
Val Ala Ala Ser Pro Arg Phe Thr Leu Pro Val Pro Gly Phe Glu Gly
145                 150                 155                 160

TAC CGC GAG CCG CTT TGC TTG AGC CCC GCT AGC AGC GGC TCC TCT GCC     528
Tyr Arg Glu Pro Leu Cys Leu Ser Pro Ala Ser Ser Gly Ser Ser Ala
                165                 170                 175

AGC TTC ATT TCT GAC ACC TTC TCC CCC TAC ACC TCG CCC TGC GTC TCG     576
```

```
Ser Phe Ile Ser Asp Thr Phe Ser Pro Tyr Thr Ser Pro Cys Val Ser
            180                 185                 190

CCC AAT AAC GGC GGG CCC GAC GAC CTG TGT CCG CAG TTT CAA AAC ATC      624
Pro Asn Asn Gly Gly Pro Asp Asp Leu Cys Pro Gln Phe Gln Asn Ile
        195                 200                 205

CCT GCT CAT TAT TCC CCC AGA ACC TCG CCA ATA ATG TCA CCT CGA ACC      672
Pro Ala His Tyr Ser Pro Arg Thr Ser Pro Ile Met Ser Pro Arg Thr
    210                 215                 220

AGC CTC GCC GAG GAC AGC TGC CTG GGC CGC CAC TCG CCC GTG CCC CGT      720
Ser Leu Ala Glu Asp Ser Cys Leu Gly Arg His Ser Pro Val Pro Arg
225                 230                 235                 240

CCG GCC TCC CGC TCC TCA TCG CCT GGT GCC AAG CGG AGG CAT TCG TGC      768
Pro Ala Ser Arg Ser Ser Ser Pro Gly Ala Lys Arg Arg His Ser Cys
                245                 250                 255

GCC GAG GCC TTG GTT GCC CTG CCG CCC GGA GCC TCA CCC CAG CGC TCC      816
Ala Glu Ala Leu Val Ala Leu Pro Pro Gly Ala Ser Pro Gln Arg Ser
            260                 265                 270

CGG AGC CCC TCG CCG CAG CCC TCA TCT CAC GTG GCA CCC CAG GAC CAC      864
Arg Ser Pro Ser Pro Gln Pro Ser Ser His Val Ala Pro Gln Asp His
        275                 280                 285

GGC TCC CCG GCT GGG TAC CCC CCT GTG GCT GGC TCT GCC GTG ATC ATG      912
Gly Ser Pro Ala Gly Tyr Pro Pro Val Ala Gly Ser Ala Val Ile Met
    290                 295                 300

GAT GCC CTG AAC AGC CTC GCC ACG GAC TCG CCT TGT GGG ATC CCC CCC      960
Asp Ala Leu Asn Ser Leu Ala Thr Asp Ser Pro Cys Gly Ile Pro Pro
305                 310                 315                 320

AAG ATG TGG AAG ACC AGC CCT GAC CCC TCG CCG GTG TCT GCC GCC CCA     1008
Lys Met Trp Lys Thr Ser Pro Asp Pro Ser Pro Val Ser Ala Ala Pro
                325                 330                 335

TCC AAG GCC GGC CTG CCT CGC CAC ATC TAC CCG GCC GTG GAG TTC CTG     1056
Ser Lys Ala Gly Leu Pro Arg His Ile Tyr Pro Ala Val Glu Phe Leu
            340                 345                 350

GGG CCC TGC GAG CAG GGC GAG AGG AGA AAC TCG GCT CCA GAA TCC ATC     1104
Gly Pro Cys Glu Gln Gly Glu Arg Arg Asn Ser Ala Pro Glu Ser Ile
        355                 360                 365

CTG CTG GTT CCG CCC ACT TGG CCC AAG CCG CTG GTG CCT GCC ATT CCC     1152
Leu Leu Val Pro Pro Thr Trp Pro Lys Pro Leu Val Pro Ala Ile Pro
    370                 375                 380

ATC TGC AGC ATC CCA GTG ACT GCA TCC CTC CCT CCA CTT GAG TGG CCG     1200
Ile Cys Ser Ile Pro Val Thr Ala Ser Leu Pro Pro Leu Glu Trp Pro
385                 390                 395                 400

CTG TCC AGT CAG TCA GGC TCT TAC GAG CTG CGG ATC GAG GTG CAG CCC     1248
Leu Ser Ser Gln Ser Gly Ser Tyr Glu Leu Arg Ile Glu Val Gln Pro
                405                 410                 415
```

AAG CCA CAT CAC CGG GCC CAC TAT GAG ACA GAA GGC AGC CGA GGG GCT 1296
Lys Pro His His Arg Ala His Tyr Glu Thr Glu Gly Ser Arg Gly Ala
420 425 430

GTC AAA GCT CCA ACT GGA GGC CAC CCT GTG GTT CAG CTC CAT GGC TAC 1344
Val Lys Ala Pro Thr Gly Gly His Pro Val Val Gln Leu His Gly Tyr
435 440 445

ATG GAA AAC AAG CCT CTG GGA CTT CAG ATC TTC ATT GGG ACA GCT GAT 1392
Met Glu Asn Lys Pro Leu Gly Leu Gln Ile Phe Ile Gly Thr Ala Asp
450 455 460

GAG CGG ATC CTT AAG CCG CAC GCC TTC TAC CAG GTG CAC CGA ATC ACG 1440
Glu Arg Ile Leu Lys Pro His Ala Phe Tyr Gln Val His Arg Ile Thr
465 470 475 480

GGG AAA ACT GTC ACC ACC ACC AGC TAT GAG AAG ATA GTG GGC AAC ACC 1488
Gly Lys Thr Val Thr Thr Thr Ser Tyr Glu Lys Ile Val Gly Asn Thr
485 490 495

AAA GTC CTG GAG ATC CCC TTG GAG CCC AAA AAC AAC ATG AGG GCA ACC 1536
Lys Val Leu Glu Ile Pro Leu Glu Pro Lys Asn Asn Met Arg Ala Thr
500 505 510

ATC GAC TGT GCG GGG ATC TTG AAG CTT AGA AAC GCC GAC ATT GAG CTG 1584
Ile Asp Cys Ala Gly Ile Leu Lys Leu Arg Asn Ala Asp Ile Glu Leu
515 520 525

CGG AAA GGC GAG ACG GAC ATT GGA AGA AAG AAC ACG CGG GTG AGA CTG 1632
Arg Lys Gly Glu Thr Asp Ile Gly Arg Lys Asn Thr Arg Val Arg Leu
530 535 540

GTT TTC CGA GTT CAC ATC CCA GAG TCC AGT GGC AGA ATC GTC TCT TTA 1680
Val Phe Arg Val His Ile Pro Glu Ser Ser Gly Arg Ile Val Ser Leu
545 550 555 560

CAG ACT GCA TCT AAC CCC ATC GAG TGC TCC CAG CGA TCT GCT CAC GAG 1728
Gln Thr Ala Ser Asn Pro Ile Glu Cys Ser Gln Arg Ser Ala His Glu
565 570 575

CTG CCC ATG GTT GAA AGA CAA GAC ACA GAC AGC TGC CTG GTC TAT GGC 1776
Leu Pro Met Val Glu Arg Gln Asp Thr Asp Ser Cys Leu Val Tyr Gly
580 585 590

GGC CAG CAA ATG ATC CTC ACG GGG CAG AAC TTT ACA TCC GAG TCC AAA 1824
Gly Gln Gln Met Ile Leu Thr Gly Gln Asn Phe Thr Ser Glu Ser Lys
595 600 605

GTT GTG TTT ACT GAG AAG ACC ACA GAT GGA CAG CAA ATT TGG GAG ATG 1872
Val Val Phe Thr Glu Lys Thr Thr Asp Gly Gln Gln Ile Trp Glu Met
610 615 620

GAA GCC ACG GTG GAT AAG GAC AAG AGC CAG CCC AAC ATG CTT TTT GTT 1920
Glu Ala Thr Val Asp Lys Asp Lys Ser Gln Pro Asn Met Leu Phe Val
625 630 635 640

GAG ATC CCT GAA TAT CGG AAC AAG CAT ATC CGC ACA CCT GTA AAA GTG 1968

Glu Ile Pro Glu Tyr Arg Asn Lys His Ile Arg Thr Pro Val Lys Val
645 650 655

AAC TTC TAC GTC ATC AAT GGG AAG AGA AAA CGA AGT CAG CCT CAG CAC 2016
Asn Phe Tyr Val Ile Asn Gly Lys Arg Lys Arg Ser Gln Pro Gln His
660 665 670

TTT ACC TAC CAC CCA GTC CCA GCC ATC AAG ACG GAG CCC ACG GAT GAA 2064
Phe Thr Tyr His Pro Val Pro Ala Ile Lys Thr Glu Pro Thr Asp Glu
675 680 685

TAT GAC CCC ACT CTG ATC TGC AGC CCC ACC CAT GGA GGC CTG GGG AGC 2112
Tyr Asp Pro Thr Leu Ile Cys Ser Pro Thr His Gly Gly Leu Gly Ser
690 695 700

CAG CCT TAC TAC CCC CAG CAC CCG ATG GTG GCC GAG TCC CCC TCC TGC 2160
Gln Pro Tyr Tyr Pro Gln His Pro Met Val Ala Glu Ser Pro Ser Cys
705 710 715 720

CTC GTG GCC ACC ATG GCT CCC TGC CAG CAG TTC CGC ACG GGG CTC TCA 2208
Leu Val Ala Thr Met Ala Pro Cys Gln Gln Phe Arg Thr Gly Leu Ser
725 730 735

TCC CCT GAC GCC CGC TAC CAG CAA CAG AAC CCA GCG GCC GTA CTC TAC 2256
Ser Pro Asp Ala Arg Tyr Gln Gln Gln Asn Pro Ala Ala Val Leu Tyr
740 745 750

CAG CGG AGC AAG AGC CTG AGC CCC AGC CTG CTG GGC TAT CAG CAG CCG 2304
Gln Arg Ser Lys Ser Leu Ser Pro Ser Leu Leu Gly Tyr Gln Gln Pro
755 760 765

GCC CTC ATG GCC GCC CCG CTG TCC CTT GCG GAC GCT CAC CGC TCT GTG 2352
Ala Leu Met Ala Ala Pro Leu Ser Leu Ala Asp Ala His Arg Ser Val
770 775 780

CTG GTG CAC GCC GGC TCC CAG GGC CAG AGC TCA GCC CTG CTC CAC CCC 2400
Leu Val His Ala Gly Ser Gln Gly Gln Ser Ser Ala Leu Leu His Pro
785 790 795 800

TCT CCG ACC AAC CAG CAG GCC TCG CCT GTG ATC CAC TAC TCA CCC ACC 2448
Ser Pro Thr Asn Gln Gln Ala Ser Pro Val Ile His Tyr Ser Pro Thr
805 810 815

AAC CAG CAG CTG CGC TGC GGA AGC CAC CAG GAG TTC CAG CAC ATC ATG 2496
Asn Gln Gln Leu Arg Cys Gly Ser His Gln Glu Phe Gln His Ile Met
820 825 830

TAC TGC GAG AAT TTC GCA CCA GGC ACC ACC AGA CCT GGC CCG CCC CCG 2544
Tyr Cys Glu Asn Phe Ala Pro Gly Thr Thr Arg Pro Gly Pro Pro Pro
835 840 845

GTC AGT CAA GGT CAG AGG CTG AGC CCG GGT TCC TAC CCC ACA GTC ATT 2592
Val Ser Gln Gly Gln Arg Leu Ser Pro Gly Ser Tyr Pro Thr Val Ile
850 855 860

CAG CAG CAG AAT GCC ACG AGC CAA AGA GCC GCC AAA AAC GGA CCC CCG 2640
Gln Gln Gln Asn Ala Thr Ser Gln Arg Ala Ala Lys Asn Gly Pro Pro
865 870 875 880

```
GTC AGT GAC CAA AAG GAA GTA TTA CCT GCG GGG GTG ACC ATT AAA CAG     2688
Val Ser Asp Gln Lys Glu Val Leu Pro Ala Gly Val Thr Ile Lys Gln
                885                 890                 895

GAG CAG AAC TTG GAC CAG ACC TAC TTG GAT GAT GTT AAT GAA ATT ATC     2736
Glu Gln Asn Leu Asp Gln Thr Tyr Leu Asp Asp Val Asn Glu Ile Ile
            900                 905                 910

AGG AAG GAG TTT TCA GGA CCT CCT GCC AGA AAT CAG ACG AGA ATT CTG     2784
Arg Lys Glu Phe Ser Gly Pro Pro Ala Arg Asn Gln Thr Arg Ile Leu
        915                 920                 925

CAG TCG ACG GTA CCG CGG GCC CGG GAT CCA CCG GTC GCC ACC ATG GTG     2832
Gln Ser Thr Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val
    930                 935                 940

AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG     2880
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
945                 950                 955                 960

CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC     2928
Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
                965                 970                 975

GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC     2976
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
            980                 985                 990

ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC     3024
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
        995                 1000                1005

TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC     3072
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
    1010                1015                1020

GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC     3120
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
1025                1030                1035                1040

ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG     3168
Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
                1045                1050                1055

TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC     3216
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
            1060                1065                1070

TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC     3264
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
        1075                1080                1085

AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC     3312
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
    1090                1095                1100

AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG     3360
```

Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
1105 1110 1115 1120

CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG 3408
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
1125 1130 1135

CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA 3456
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
1140 1145 1150

GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC 3504
Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
1155 1160 1165

GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 3546
Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
1170 1175 1180

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1181 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Met Asn Ala Pro Glu Arg Gln Pro Gln Pro Asp Gly Gly Asp Ala Pro
1 5 10 15
Gly His Glu Pro Gly Gly Ser Pro Gln Asp Glu Leu Asp Phe Ser Ile
20 25 30
Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn Glu Glu Glu Pro Asn Ala
35 40 45
His Lys Val Ala Ser Pro Pro Ser Gly Pro Ala Tyr Pro Asp Asp Val
50 55 60
Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro Leu Ala Ser Leu Ser Gly
65 70 75 80
Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp Arg Val Gly Pro Gln Lys
85 90 95
Phe Leu Ser Ala Ala Lys Pro Ala Gly Ala Ser Gly Leu Ser Pro Arg
100 105 110
Ile Glu Ile Thr Pro Ser His Glu Leu Ile Gln Ala Val Gly Pro Leu
115 120 125
Arg Met Arg Asp Ala Gly Leu Leu Val Glu Gln Pro Pro Leu Ala Gly
130 135 140
Val Ala Ala Ser Pro Arg Phe Thr Leu Pro Val Pro Gly Phe Glu Gly
145 150 155 160
Tyr Arg Glu Pro Leu Cys Leu Ser Pro Ala Ser Ser Gly Ser Ser Ala
165 170 175
Ser Phe Ile Ser Asp Thr Phe Ser Pro Tyr Thr Ser Pro Cys Val Ser
180 185 190
Pro Asn Asn Gly Gly Pro Asp Asp Leu Cys Pro Gln Phe Gln Asn Ile

195 200 205
Pro Ala His Tyr Ser Pro Arg Thr Ser Pro Ile Met Ser Pro Arg Thr
210 215 220
Ser Leu Ala Glu Asp Ser Cys Leu Gly Arg His Ser Pro Val Pro Arg
225 230 235 240
Pro Ala Ser Arg Ser Ser Ser Pro Gly Ala Lys Arg Arg His Ser Cys
245 250 255
Ala Glu Ala Leu Val Ala Leu Pro Pro Gly Ala Ser Pro Gln Arg Ser
260 265 270
Arg Ser Pro Ser Pro Gln Pro Ser Ser His Val Ala Pro Gln Asp His
275 280 285
Gly Ser Pro Ala Gly Tyr Pro Pro Val Ala Gly Ser Ala Val Ile Met
290 295 300
Asp Ala Leu Asn Ser Leu Ala Thr Asp Ser Pro Cys Gly Ile Pro Pro
305 310 315 320
Lys Met Trp Lys Thr Ser Pro Asp Pro Ser Pro Val Ser Ala Ala Pro
325 330 335
Ser Lys Ala Gly Leu Pro Arg His Ile Tyr Pro Ala Val Glu Phe Leu
340 345 350
Gly Pro Cys Glu Gln Gly Glu Arg Arg Asn Ser Ala Pro Glu Ser Ile
355 360 365
Leu Leu Val Pro Pro Thr Trp Pro Lys Pro Leu Val Pro Ala Ile Pro
370 375 380
Ile Cys Ser Ile Pro Val Thr Ala Ser Leu Pro Pro Leu Glu Trp Pro
385 390 395 400
Leu Ser Ser Gln Ser Gly Ser Tyr Glu Leu Arg Ile Glu Val Gln Pro
405 410 415
Lys Pro His His Arg Ala His Tyr Glu Thr Glu Gly Ser Arg Gly Ala
420 425 430
Val Lys Ala Pro Thr Gly Gly His Pro Val Val Gln Leu His Gly Tyr
435 440 445
Met Glu Asn Lys Pro Leu Gly Leu Gln Ile Phe Ile Gly Thr Ala Asp
450 455 460
Glu Arg Ile Leu Lys Pro His Ala Phe Tyr Gln Val His Arg Ile Thr
465 470 475 480
Gly Lys Thr Val Thr Thr Thr Ser Tyr Glu Lys Ile Val Gly Asn Thr
485 490 495
Lys Val Leu Glu Ile Pro Leu Glu Pro Lys Asn Asn Met Arg Ala Thr
500 505 510
Ile Asp Cys Ala Gly Ile Leu Lys Leu Arg Asn Ala Asp Ile Glu Leu
515 520 525
Arg Lys Gly Glu Thr Asp Ile Gly Arg Lys Asn Thr Arg Val Arg Leu
530 535 540
Val Phe Arg Val His Ile Pro Glu Ser Ser Gly Arg Ile Val Ser Leu
545 550 555 560
Gln Thr Ala Ser Asn Pro Ile Glu Cys Ser Gln Arg Ser Ala His Glu
565 570 575
Leu Pro Met Val Glu Arg Gln Asp Thr Asp Ser Cys Leu Val Tyr Gly
580 585 590
Gly Gln Gln Met Ile Leu Thr Gly Gln Asn Phe Thr Ser Glu Ser Lys
595 600 605
Val Val Phe Thr Glu Lys Thr Thr Asp Gly Gln Gln Ile Trp Glu Met
610 615 620
Glu Ala Thr Val Asp Lys Asp Lys Ser Gln Pro Asn Met Leu Phe Val
625 630 635 640
Glu Ile Pro Glu Tyr Arg Asn Lys His Ile Arg Thr Pro Val Lys Val
645 650 655
Asn Phe Tyr Val Ile Asn Gly Lys Arg Lys Arg Ser Gln Pro Gln His

```
            660                 665                 670
Phe Thr Tyr His Pro Val Pro Ala Ile Lys Thr Glu Pro Thr Asp Glu
        675                 680                 685
Tyr Asp Pro Thr Leu Ile Cys Ser Pro Thr His Gly Gly Leu Gly Ser
    690                 695                 700
Gln Pro Tyr Tyr Pro Gln His Pro Met Val Ala Glu Ser Pro Ser Cys
705                 710                 715                 720
Leu Val Ala Thr Met Ala Pro Cys Gln Gln Phe Arg Thr Gly Leu Ser
                725                 730                 735
Ser Pro Asp Ala Arg Tyr Gln Gln Gln Asn Pro Ala Ala Val Leu Tyr
            740                 745                 750
Gln Arg Ser Lys Ser Leu Ser Pro Ser Leu Leu Gly Tyr Gln Gln Pro
        755                 760                 765
Ala Leu Met Ala Ala Pro Leu Ser Leu Ala Asp Ala His Arg Ser Val
    770                 775                 780
Leu Val His Ala Gly Ser Gln Gly Gln Ser Ser Ala Leu Leu His Pro
785                 790                 795                 800
Ser Pro Thr Asn Gln Gln Ala Ser Pro Val Ile His Tyr Ser Pro Thr
                805                 810                 815
Asn Gln Gln Leu Arg Cys Gly Ser His Gln Glu Phe Gln His Ile Met
            820                 825                 830
Tyr Cys Glu Asn Phe Ala Pro Gly Thr Thr Arg Pro Gly Pro Pro Pro
        835                 840                 845
Val Ser Gln Gly Gln Arg Leu Ser Pro Gly Ser Tyr Pro Thr Val Ile
    850                 855                 860
Gln Gln Gln Asn Ala Thr Ser Gln Arg Ala Ala Lys Asn Gly Pro Pro
865                 870                 875                 880
Val Ser Asp Gln Lys Glu Val Leu Pro Ala Gly Val Thr Ile Lys Gln
                885                 890                 895
Glu Gln Asn Leu Asp Gln Thr Tyr Leu Asp Asp Val Asn Glu Ile Ile
            900                 905                 910
Arg Lys Glu Phe Ser Gly Pro Pro Ala Arg Asn Gln Thr Arg Ile Leu
        915                 920                 925
Gln Ser Thr Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val
    930                 935                 940
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
945                 950                 955                 960
Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
                965                 970                 975
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
            980                 985                 990
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
        995                 1000                1005
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
    1010                1015                1020
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
025                 1030                1035                1040
Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
                1045                1050                1055
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
            1060                1065                1070
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
        1075                1080                1085
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
    1090                1095                1100
Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
105                 1110                1115                1120
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
```

1125 1130 1135
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
1140 1145 1150
Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
1155 1160 1165
Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
1170 1175 1180

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2802 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2799
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GGG AGC ATG GGC ACC TTG CGG GAT TTA CAG TAC 768
Gly Leu Arg Ser Arg Gly Ser Met Gly Thr Leu Arg Asp Leu Gln Tyr
245 250 255

GCG CTC CAG GAG AAG ATC GAG GAG CTG AGG CAG CGG GAT GCT CTC ATC 816
Ala Leu Gln Glu Lys Ile Glu Glu Leu Arg Gln Arg Asp Ala Leu Ile
260 265 270

GAC GAG CTG GAG CTG GAG TTG GAT CAG AAG GAC GAA CTG ATC CAG AAG 864
Asp Glu Leu Glu Leu Glu Leu Asp Gln Lys Asp Glu Leu Ile Gln Lys
275 280 285

CTG CAG AAC GAG CTG GAC AAG TAC CGC TCG GTG ATC CGA CCA GCC ACC 912
Leu Gln Asn Glu Leu Asp Lys Tyr Arg Ser Val Ile Arg Pro Ala Thr
290 295 300

CAG CAG GCG CAG AAG CAG AGC GCG AGC ACC TTG CAG GGC GAG CCG CGC 960
Gln Gln Ala Gln Lys Gln Ser Ala Ser Thr Leu Gln Gly Glu Pro Arg
305 310 315 320

ACC AAG CGG CAG GCG ATC TCC GCC GAG CCC ACC GCC TTC GAC ATC CAG 1008
Thr Lys Arg Gln Ala Ile Ser Ala Glu Pro Thr Ala Phe Asp Ile Gln
325 330 335

GAT CTC AGC CAT GTG ACC CTG CCC TTC TAC CCC AAG AGC CCA CAG TCC 1056
Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser
340 345 350

AAG GAT CTT ATA AAG GAA GCT ATC CTT GAC AAT GAC TTT ATG AAG AAC 1104
Lys Asp Leu Ile Lys Glu Ala Ile Leu Asp Asn Asp Phe Met Lys Asn
355 360 365

```
TTG GAG CTG TCG CAG ATC CAG GAG ATT GTG GAT TGT ATG TAC CCG GTG     1152
Leu Glu Leu Ser Gln Ile Gln Glu Ile Val Asp Cys Met Tyr Pro Val
    370                 375                 380

GAG TAT GGC AAG GAC AGT TGC ATC ATC AAA GAA GGA GAC GTG GGG TCA     1200
Glu Tyr Gly Lys Asp Ser Cys Ile Ile Lys Glu Gly Asp Val Gly Ser
385                 390                 395                 400

CTG GTG TAT GTC ATG GAA GAT GGT AAG GTT GAA GTT ACA AAA GAA GGT     1248
Leu Val Tyr Val Met Glu Asp Gly Lys Val Glu Val Thr Lys Glu Gly
                405                 410                 415

GTG AAG TTG TGT ACC ATG GGT CCA GGA AAA GTG TTT GGG GAA TTG GCT     1296
Val Lys Leu Cys Thr Met Gly Pro Gly Lys Val Phe Gly Glu Leu Ala
            420                 425                 430

ATT CTT TAC AAC TGT ACC CGG ACA GCG ACC GTC AAG ACT CTT GTA AAT     1344
Ile Leu Tyr Asn Cys Thr Arg Thr Ala Thr Val Lys Thr Leu Val Asn
        435                 440                 445

GTA AAA CTC TGG GCC ATT GAT CGA CAA TGT TTT CAA ACA ATA ATG ATG     1392
Val Lys Leu Trp Ala Ile Asp Arg Gln Cys Phe Gln Thr Ile Met Met
    450                 455                 460

AGG ACA GGA CTC ATC AAG CAT ACC GAG TAT ATG GAA TTT TTA AAA AGC     1440
Arg Thr Gly Leu Ile Lys His Thr Glu Tyr Met Glu Phe Leu Lys Ser
465                 470                 475                 480

GTT CCA ACA TTC CAG AGC CTT CCT GAA GAG ATC CTC AGC AAG CTT GCT     1488
Val Pro Thr Phe Gln Ser Leu Pro Glu Glu Ile Leu Ser Lys Leu Ala
                485                 490                 495

GAT GTC CTT GAA GAG ACC CAC TAT GAA AAT GGA GAA TAT ATT ATC AGG     1536
Asp Val Leu Glu Glu Thr His Tyr Glu Asn Gly Glu Tyr Ile Ile Arg
            500                 505                 510

CAA GGT GCA AGA GGG GAC ACC TTC TTT ATC ATC AGC AAA GGA ACG GTA     1584
Gln Gly Ala Arg Gly Asp Thr Phe Phe Ile Ile Ser Lys Gly Thr Val
        515                 520                 525

AAT GTC ACT CGT GAA GAC TCA CCG AGT GAA GAC CCA GTC TTT CTT AGA     1632
Asn Val Thr Arg Glu Asp Ser Pro Ser Glu Asp Pro Val Phe Leu Arg
    530                 535                 540

ACT TTA GGA AAA GGA GAC TGG TTT GGA GAG AAA GCC TTG CAG GGG GAA     1680
Thr Leu Gly Lys Gly Asp Trp Phe Gly Glu Lys Ala Leu Gln Gly Glu
545                 550                 555                 560

GAT GTG AGA ACA GCA AAC GTA ATT GCT GCA GAA GCT GTA ACC TGC CTT     1728
Asp Val Arg Thr Ala Asn Val Ile Ala Ala Glu Ala Val Thr Cys Leu
                565                 570                 575

GTG ATT GAC AGA GAC TCT TTT AAA CAT TTG ATT GGA GGG CTG GAT GAT     1776
Val Ile Asp Arg Asp Ser Phe Lys His Leu Ile Gly Gly Leu Asp Asp
            580                 585                 590

GTT TCT AAT AAA GCA TAT GAA GAT GCA GAA GCT AAA GCA AAA TAT GAA     1824
```

Val Ser Asn Lys Ala Tyr Glu Asp Ala Glu Ala Lys Ala Lys Tyr Glu
595 600 605

GCT GAA GCG GCT TTC TTC GCC AAC CTG AAG CTG TCT GAT TTC AAC ATC 1872
Ala Glu Ala Ala Phe Phe Ala Asn Leu Lys Leu Ser Asp Phe Asn Ile
610 615 620

ATT GAT ACC CTT GGA GTT GGA GGT TTC GGA CGA GTA GAA CTG GTC CAG 1920
Ile Asp Thr Leu Gly Val Gly Gly Phe Gly Arg Val Glu Leu Val Gln
625 630 635 640

TTG AAA AGT GAA GAA TCC AAA ACG TTT GCA ATG AAG ATT CTC AAG AAA 1968
Leu Lys Ser Glu Glu Ser Lys Thr Phe Ala Met Lys Ile Leu Lys Lys
645 650 655

CGT CAC ATT GTG GAC ACA AGA CAG CAG GAG CAC ATC CGC TCA GAG AAG 2016
Arg His Ile Val Asp Thr Arg Gln Gln Glu His Ile Arg Ser Glu Lys
660 665 670

CAG ATC ATG CAG GGG GCT CAT TCC GAT TTC ATA GTG AGA CTG TAC AGA 2064
Gln Ile Met Gln Gly Ala His Ser Asp Phe Ile Val Arg Leu Tyr Arg
675 680 685

ACA TTT AAG GAC AGC AAA TAT TTG TAT ATG TTG ATG GAA GCT TGT CTA 2112
Thr Phe Lys Asp Ser Lys Tyr Leu Tyr Met Leu Met Glu Ala Cys Leu
690 695 700

GGT GGA GAG CTC TGG ACC ATT CTC AGG GAT AGA GGT TCG TTT GAA GAT 2160
Gly Gly Glu Leu Trp Thr Ile Leu Arg Asp Arg Gly Ser Phe Glu Asp
705 710 715 720

TCT ACA ACC AGA TTT TAC ACA GCA TGT GTG GTA GAA GCT TTT GCC TAT 2208
Ser Thr Thr Arg Phe Tyr Thr Ala Cys Val Val Glu Ala Phe Ala Tyr
725 730 735

CTG CAT TCC AAA GGA ATC ATT TAC AGG GAC CTC AAG CCA GAA AAT CTC 2256
Leu His Ser Lys Gly Ile Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu
740 745 750

ATC CTA GAT CAC CGA GGT TAT GCC AAA CTG GTT GAT TTT GGC TTT GCA 2304
Ile Leu Asp His Arg Gly Tyr Ala Lys Leu Val Asp Phe Gly Phe Ala
755 760 765

AAG AAA ATA GGA TTT GGA AAG AAA ACA TGG ACT TTT TGT GGG ACT CCA 2352
Lys Lys Ile Gly Phe Gly Lys Lys Thr Trp Thr Phe Cys Gly Thr Pro
770 775 780

GAG TAT GTA GCC CCA GAG ATC ATC CTG AAC AAA GGC CAT GAC ATT TCA 2400
Glu Tyr Val Ala Pro Glu Ile Ile Leu Asn Lys Gly His Asp Ile Ser
785 790 795 800

GCC GAC TAC TGG TCA CTG GGA ATC CTA ATG TAT GAA CTC CTG ACT GGC 2448
Ala Asp Tyr Trp Ser Leu Gly Ile Leu Met Tyr Glu Leu Leu Thr Gly
805 810 815

AGC CCA CCT TTC TCA GGC CCA GAT CCT ATG AAA ACC TAT AAC ATC ATA 2496
Ser Pro Pro Phe Ser Gly Pro Asp Pro Met Lys Thr Tyr Asn Ile Ile
820 825 830

TTG AGG GGG ATT GAC ATG ATA GAA TTT CCA AAG AAG ATT GCC AAA AAT 2544
Leu Arg Gly Ile Asp Met Ile Glu Phe Pro Lys Lys Ile Ala Lys Asn
835 840 845

GCT GCT AAT TTA ATT AAA AAA CTA TGC AGG GAC AAT CCA TCA GAA AGA 2592
Ala Ala Asn Leu Ile Lys Lys Leu Cys Arg Asp Asn Pro Ser Glu Arg
850 855 860

TTA GGG AAT TTG AAA AAT GGA GTA AAA GAC ATT CAA AAG CAC AAA TGG 2640
Leu Gly Asn Leu Lys Asn Gly Val Lys Asp Ile Gln Lys His Lys Trp
865 870 875 880

TTT GAG GGC TTT AAC TGG GAA GGC TTA AGA AAA GGT ACC TTG ACA CCT 2688
Phe Glu Gly Phe Asn Trp Glu Gly Leu Arg Lys Gly Thr Leu Thr Pro
885 890 895

CCT ATA ATA CCA AGT GTT GCA TCA CCC ACA GAC ACA AGT AAT TTT GAC 2736
Pro Ile Ile Pro Ser Val Ala Ser Pro Thr Asp Thr Ser Asn Phe Asp
900 905 910

AGT TTC CCT GAG GAC AAC GAT GAA CCA CCA CCT GAT GAC AAC TCA GGA 2784
Ser Phe Pro Glu Asp Asn Asp Glu Pro Pro Pro Asp Asp Asn Ser Gly
915 920 925

TGG GAT ATA GAC TTC TAA 2802
Trp Asp Ile Asp Phe
930

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 933 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly

115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Gly Ser Met Gly Thr Leu Arg Asp Leu Gln Tyr
245 250 255
Ala Leu Gln Glu Lys Ile Glu Glu Leu Arg Gln Arg Asp Ala Leu Ile
260 265 270
Asp Glu Leu Glu Leu Glu Leu Asp Gln Lys Asp Glu Leu Ile Gln Lys
275 280 285
Leu Gln Asn Glu Leu Asp Lys Tyr Arg Ser Val Ile Arg Pro Ala Thr
290 295 300
Gln Gln Ala Gln Lys Gln Ser Ala Ser Thr Leu Gln Gly Glu Pro Arg
305 310 315 320
Thr Lys Arg Gln Ala Ile Ser Ala Glu Pro Thr Ala Phe Asp Ile Gln
325 330 335
Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser
340 345 350
Lys Asp Leu Ile Lys Glu Ala Ile Leu Asp Asn Asp Phe Met Lys Asn
355 360 365
Leu Glu Leu Ser Gln Ile Gln Glu Ile Val Asp Cys Met Tyr Pro Val
370 375 380
Glu Tyr Gly Lys Asp Ser Cys Ile Ile Lys Glu Gly Asp Val Gly Ser
385 390 395 400
Leu Val Tyr Val Met Glu Asp Gly Lys Val Glu Val Thr Lys Glu Gly
405 410 415
Val Lys Leu Cys Thr Met Gly Pro Gly Lys Val Phe Gly Glu Leu Ala
420 425 430
Ile Leu Tyr Asn Cys Thr Arg Thr Ala Thr Val Lys Thr Leu Val Asn
435 440 445
Val Lys Leu Trp Ala Ile Asp Arg Gln Cys Phe Gln Thr Ile Met Met
450 455 460
Arg Thr Gly Leu Ile Lys His Thr Glu Tyr Met Glu Phe Leu Lys Ser
465 470 475 480
Val Pro Thr Phe Gln Ser Leu Pro Glu Glu Ile Leu Ser Lys Leu Ala
485 490 495
Asp Val Leu Glu Glu Thr His Tyr Glu Asn Gly Glu Tyr Ile Ile Arg
500 505 510
Gln Gly Ala Arg Gly Asp Thr Phe Phe Ile Ile Ser Lys Gly Thr Val
515 520 525
Asn Val Thr Arg Glu Asp Ser Pro Ser Glu Asp Pro Val Phe Leu Arg
530 535 540
Thr Leu Gly Lys Gly Asp Trp Phe Gly Glu Lys Ala Leu Gln Gly Glu
545 550 555 560
Asp Val Arg Thr Ala Asn Val Ile Ala Ala Glu Ala Val Thr Cys Leu
565 570 575
Val Ile Asp Arg Asp Ser Phe Lys His Leu Ile Gly Gly Leu Asp Asp

580 585 590
Val Ser Asn Lys Ala Tyr Glu Asp Ala Glu Ala Lys Ala Lys Tyr Glu
595 600 605
Ala Glu Ala Ala Phe Phe Ala Asn Leu Lys Leu Ser Asp Phe Asn Ile
610 615 620
Ile Asp Thr Leu Gly Val Gly Gly Phe Gly Arg Val Glu Leu Val Gln
625 630 635 640
Leu Lys Ser Glu Glu Ser Lys Thr Phe Ala Met Lys Ile Leu Lys Lys
645 650 655
Arg His Ile Val Asp Thr Arg Gln Gln Glu His Ile Arg Ser Glu Lys
660 665 670
Gln Ile Met Gln Gly Ala His Ser Asp Phe Ile Val Arg Leu Tyr Arg
675 680 685
Thr Phe Lys Asp Ser Lys Tyr Leu Tyr Met Leu Met Glu Ala Cys Leu
690 695 700
Gly Gly Glu Leu Trp Thr Ile Leu Arg Asp Arg Gly Ser Phe Glu Asp
705 710 715 720
Ser Thr Thr Arg Phe Tyr Thr Ala Cys Val Val Glu Ala Phe Ala Tyr
725 730 735
Leu His Ser Lys Gly Ile Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu
740 745 750
Ile Leu Asp His Arg Gly Tyr Ala Lys Leu Val Asp Phe Gly Phe Ala
755 760 765
Lys Lys Ile Gly Phe Gly Lys Lys Thr Trp Thr Phe Cys Gly Thr Pro
770 775 780
Glu Tyr Val Ala Pro Glu Ile Ile Leu Asn Lys Gly His Asp Ile Ser
785 790 795 800
Ala Asp Tyr Trp Ser Leu Gly Ile Leu Met Tyr Glu Leu Leu Thr Gly
805 810 815
Ser Pro Pro Phe Ser Gly Pro Asp Pro Met Lys Thr Tyr Asn Ile Ile
820 825 830
Leu Arg Gly Ile Asp Met Ile Glu Phe Pro Lys Lys Ile Ala Lys Asn
835 840 845
Ala Ala Asn Leu Ile Lys Lys Leu Cys Arg Asp Asn Pro Ser Glu Arg
850 855 860
Leu Gly Asn Leu Lys Asn Gly Val Lys Asp Ile Gln Lys His Lys Trp
865 870 875 880
Phe Glu Gly Phe Asn Trp Glu Gly Leu Arg Lys Gly Thr Leu Thr Pro
885 890 895
Pro Ile Ile Pro Ser Val Ala Ser Pro Thr Asp Thr Ser Asn Phe Asp
900 905 910
Ser Phe Pro Glu Asp Asn Asp Glu Pro Pro Pro Asp Asp Asn Ser Gly
915 920 925
Trp Asp Ile Asp Phe
930

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2799 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2795
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

```
ATG GGC ACC TTG CGG GAT TTA CAG TAC GCG CTC CAG GAG AAG ATC GAG      48
Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu
 1               5                  10                  15

GAG CTG AGG CAG CGG GAT GCT CTC ATC GAC GAG CTG GAG CTG GAG TTG      96
Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu
            20                  25                  30

GAT CAG AAG GAC GAA CTG ATC CAG AAG CTG CAG AAC GAG CTG GAC AAG     144
Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys
        35                  40                  45

TAC CGC TCG GTG ATC CGA CCA GCC ACC CAG CAG GCG CAG AAG CAG AGC     192
Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser
    50                  55                  60

GCG AGC ACC TTG CAG GGC GAG CCG CGC ACC AAG CGG CAG GCG ATC TCC     240
Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser
65                  70                  75                  80

GCC GAG CCC ACC GCC TTC GAC ATC CAG GAT CTC AGC CAT GTG ACC CTG     288
Ala Glu Pro Thr Ala Phe Asp Ile Gln Asp Leu Ser His Val Thr Leu
                85                  90                  95

CCC TTC TAC CCC AAG AGC CCA CAG TCC AAG GAT CTT ATA AAG GAA GCT     336
Pro Phe Tyr Pro Lys Ser Pro Gln Ser Lys Asp Leu Ile Lys Glu Ala
            100                 105                 110

ATC CTT GAC AAT GAC TTT ATG AAG AAC TTG GAG CTG TCG CAG ATC CAG     384
Ile Leu Asp Asn Asp Phe Met Lys Asn Leu Glu Leu Ser Gln Ile Gln
        115                 120                 125

GAG ATT GTG GAT TGT ATG TAC CCG GTG GAG TAT GGC AAG GAC AGT TGC     432
Glu Ile Val Asp Cys Met Tyr Pro Val Glu Tyr Gly Lys Asp Ser Cys
    130                 135                 140

ATC ATC AAA GAA GGA GAC GTG GGG TCA CTG GTG TAT GTC ATG GAA GAT     480
Ile Ile Lys Glu Gly Asp Val Gly Ser Leu Val Tyr Val Met Glu Asp
145                 150                 155                 160

GGT AAG GTT GAA GTT ACA AAA GAA GGT GTG AAG TTG TGT ACC ATG GGT     528
Gly Lys Val Glu Val Thr Lys Glu Gly Val Lys Leu Cys Thr Met Gly
                165                 170                 175

CCA GGA AAA GTG TTT GGG GAA TTG GCT ATT CTT TAC AAC TGT ACC CGG     576
Pro Gly Lys Val Phe Gly Glu Leu Ala Ile Leu Tyr Asn Cys Thr Arg
            180                 185                 190

ACA GCG ACC GTC AAG ACT CTT GTA AAT GTA AAA CTC TGG GCC ATT GAT     624
Thr Ala Thr Val Lys Thr Leu Val Asn Val Lys Leu Trp Ala Ile Asp
        195                 200                 205

CGA CAA TGT TTT CAA ACA ATA ATG ATG AGG ACA GGA CTC ATC AAG CAT     672
```

Arg Gln Cys Phe Gln Thr Ile Met Met Arg Thr Gly Leu Ile Lys His
210 215 220

ACC GAG TAT ATG GAA TTT TTA AAA AGC GTT CCA ACA TTC CAG AGC CTT 720
Thr Glu Tyr Met Glu Phe Leu Lys Ser Val Pro Thr Phe Gln Ser Leu
225 230 235 240

CCT GAA GAG ATC CTC AGC AAG CTT GCT GAT GTC CTT GAA GAG ACC CAC 768
Pro Glu Glu Ile Leu Ser Lys Leu Ala Asp Val Leu Glu Glu Thr His
245 250 255

TAT GAA AAT GGA GAA TAT ATT ATC AGG CAA GGT GCA AGA GGG GAC ACC 816
Tyr Glu Asn Gly Glu Tyr Ile Ile Arg Gln Gly Ala Arg Gly Asp Thr
260 265 270

TTC TTT ATC ATC AGC AAA GGA ACG GTA AAT GTC ACT CGT GAA GAC TCA 864
Phe Phe Ile Ile Ser Lys Gly Thr Val Asn Val Thr Arg Glu Asp Ser
275 280 285

CCG AGT GAA GAC CCA GTC TTT CTT AGA ACT TTA GGA AAA GGA GAC TGG 912
Pro Ser Glu Asp Pro Val Phe Leu Arg Thr Leu Gly Lys Gly Asp Trp
290 295 300

TTT GGA GAG AAA GCC TTG CAG GGG GAA GAT GTG AGA ACA GCA AAC GTA 960
Phe Gly Glu Lys Ala Leu Gln Gly Glu Asp Val Arg Thr Ala Asn Val
305 310 315 320

ATT GCT GCA GAA GCT GTA ACC TGC CTT GTG ATT GAC AGA GAC TCT TTT 1008
Ile Ala Ala Glu Ala Val Thr Cys Leu Val Ile Asp Arg Asp Ser Phe
325 330 335

AAA CAT TTG ATT GGA GGG CTG GAT GAT GTT TCT AAT AAA GCA TAT GAA 1056
Lys His Leu Ile Gly Gly Leu Asp Asp Val Ser Asn Lys Ala Tyr Glu
340 345 350

GAT GCA GAA GCT AAA GCA AAA TAT GAA GCT GAA GCG GCT TTC TTC GCC 1104
Asp Ala Glu Ala Lys Ala Lys Tyr Glu Ala Glu Ala Ala Phe Phe Ala
355 360 365

AAC CTG AAG CTG TCT GAT TTC AAC ATC ATT GAT ACC CTT GGA GTT GGA 1152
Asn Leu Lys Leu Ser Asp Phe Asn Ile Ile Asp Thr Leu Gly Val Gly
370 375 380

GGT TTC GGA CGA GTA GAA CTG GTC CAG TTG AAA AGT GAA GAA TCC AAA 1200
Gly Phe Gly Arg Val Glu Leu Val Gln Leu Lys Ser Glu Glu Ser Lys
385 390 395 400

ACG TTT GCA ATG AAG ATT CTC AAG AAA CGT CAC ATT GTG GAC ACA AGA 1248
Thr Phe Ala Met Lys Ile Leu Lys Lys Arg His Ile Val Asp Thr Arg
405 410 415

CAG CAG GAG CAC ATC CGC TCA GAG AAG CAG ATC ATG CAG GGG GCT CAT 1296
Gln Gln Glu His Ile Arg Ser Glu Lys Gln Ile Met Gln Gly Ala His
420 425 430

TCC GAT TTC ATA GTG AGA CTG TAC AGA ACA TTT AAG GAC AGC AAA TAT 1344
Ser Asp Phe Ile Val Arg Leu Tyr Arg Thr Phe Lys Asp Ser Lys Tyr
435 440 445

```
TTG TAT ATG TTG ATG GAA GCT TGT CTA GGT GGA GAG CTC TGG ACC ATT     1392
Leu Tyr Met Leu Met Glu Ala Cys Leu Gly Gly Glu Leu Trp Thr Ile
    450                 455                 460

CTC AGG GAT AGA GGT TCG TTT GAA GAT TCT ACA ACC AGA TTT TAC ACA     1440
Leu Arg Asp Arg Gly Ser Phe Glu Asp Ser Thr Thr Arg Phe Tyr Thr
465                 470                 475                 480

GCA TGT GTG GTA GAA GCT TTT GCC TAT CTG CAT TCC AAA GGA ATC ATT     1488
Ala Cys Val Val Glu Ala Phe Ala Tyr Leu His Ser Lys Gly Ile Ile
                485                 490                 495

TAC AGG GAC CTC AAG CCA GAA AAT CTC ATC CTA GAT CAC CGA GGT TAT     1536
Tyr Arg Asp Leu Lys Pro Glu Asn Leu Ile Leu Asp His Arg Gly Tyr
            500                 505                 510

GCC AAA CTG GTT GAT TTT GGC TTT GCA AAG AAA ATA GGA TTT GGA AAG     1584
Ala Lys Leu Val Asp Phe Gly Phe Ala Lys Lys Ile Gly Phe Gly Lys
        515                 520                 525

AAA ACA TGG ACT TTT TGT GGG ACT CCA GAG TAT GTA GCC CCA GAG ATC     1632
Lys Thr Trp Thr Phe Cys Gly Thr Pro Glu Tyr Val Ala Pro Glu Ile
    530                 535                 540

ATC CTG AAC AAA GGC CAT GAC ATT TCA GCC GAC TAC TGG TCA CTG GGA     1680
Ile Leu Asn Lys Gly His Asp Ile Ser Ala Asp Tyr Trp Ser Leu Gly
545                 550                 555                 560

ATC CTA ATG TAT GAA CTC CTG ACT GGC AGC CCA CCT TTC TCA GGC CCA     1728
Ile Leu Met Tyr Glu Leu Leu Thr Gly Ser Pro Pro Phe Ser Gly Pro
                565                 570                 575

GAT CCT ATG AAA ACC TAT AAC ATC ATA TTG AGG GGG ATT GAC ATG ATA     1776
Asp Pro Met Lys Thr Tyr Asn Ile Ile Leu Arg Gly Ile Asp Met Ile
            580                 585                 590

GAA TTT CCA AAG AAG ATT GCC AAA AAT GCT GCT AAT TTA ATT AAA AAA     1824
Glu Phe Pro Lys Lys Ile Ala Lys Asn Ala Ala Asn Leu Ile Lys Lys
        595                 600                 605

CTA TGC AGG GAC AAT CCA TCA GAA AGA TTA GGG AAT TTG AAA AAT GGA     1872
Leu Cys Arg Asp Asn Pro Ser Glu Arg Leu Gly Asn Leu Lys Asn Gly
    610                 615                 620

GTA AAA GAC ATT CAA AAG CAC AAA TGG TTT GAG GGC TTT AAC TGG GAA     1920
Val Lys Asp Ile Gln Lys His Lys Trp Phe Glu Gly Phe Asn Trp Glu
625                 630                 635                 640

GGC TTA AGA AAA GGT ACC TTG ACA CCT CCT ATA ATA CCA AGT GTT GCA     1968
Gly Leu Arg Lys Gly Thr Leu Thr Pro Pro Ile Ile Pro Ser Val Ala
                645                 650                 655

TCA CCC ACA GAC ACA AGT AAT TTT GAC AGT TTC CCT GAG GAC AAC GAT     2016
Ser Pro Thr Asp Thr Ser Asn Phe Asp Ser Phe Pro Glu Asp Asn Asp
            660                 665                 670

GAA CCA CCA CCT GAT GAC AAC TCA GGA TGG GAT ATA GAC TTC TCG GAT     2064
```

Glu Pro Pro Pro Asp Asp Asn Ser Gly Trp Asp Ile Asp Phe Ser Asp
675 680 685

CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG 2112
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
690 695 700

GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG 2160
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
705 710 715 720

TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG 2208
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
725 730 735

ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC 2256
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
740 745 750

ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC 2304
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
755 760 765

CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA 2352
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
770 775 780

GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC 2400
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
785 790 795 800

AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC 2448
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
805 810 815

ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG 2496
Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
820 825 830

CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC 2544
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
835 840 845

GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC 2592
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
850 855 860

ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC 2640
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
865 870 875 880

CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC 2688
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
885 890 895

ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG 2736
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
900 905 910

GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC 2784
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
915 920 925

GAG CTG TAC AA GTAA 2799
Glu Leu Tyr Lys
930

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 932 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu
1 5 10 15
Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu
20 25 30
Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys
35 40 45
Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser
50 55 60
Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser
65 70 75 80
Ala Glu Pro Thr Ala Phe Asp Ile Gln Asp Leu Ser His Val Thr Leu
85 90 95
Pro Phe Tyr Pro Lys Ser Pro Gln Ser Lys Asp Leu Ile Lys Glu Ala
100 105 110
Ile Leu Asp Asn Asp Phe Met Lys Asn Leu Glu Leu Ser Gln Ile Gln
115 120 125
Glu Ile Val Asp Cys Met Tyr Pro Val Glu Tyr Gly Lys Asp Ser Cys
130 135 140
Ile Ile Lys Glu Gly Asp Val Gly Ser Leu Val Tyr Val Met Glu Asp
145 150 155 160
Gly Lys Val Glu Val Thr Lys Glu Gly Val Lys Leu Cys Thr Met Gly
165 170 175
Pro Gly Lys Val Phe Gly Glu Leu Ala Ile Leu Tyr Asn Cys Thr Arg
180 185 190
Thr Ala Thr Val Lys Thr Leu Val Asn Val Lys Leu Trp Ala Ile Asp
195 200 205
Arg Gln Cys Phe Gln Thr Ile Met Met Arg Thr Gly Leu Ile Lys His
210 215 220
Thr Glu Tyr Met Glu Phe Leu Lys Ser Val Pro Thr Phe Gln Ser Leu
225 230 235 240
Pro Glu Glu Ile Leu Ser Lys Leu Ala Asp Val Leu Glu Glu Thr His
245 250 255
Tyr Glu Asn Gly Glu Tyr Ile Ile Arg Gln Gly Ala Arg Gly Asp Thr
260 265 270
Phe Phe Ile Ile Ser Lys Gly Thr Val Asn Val Thr Arg Glu Asp Ser

275 280 285
Pro Ser Glu Asp Pro Val Phe Leu Arg Thr Leu Gly Lys Gly Asp Trp
290 295 300
Phe Gly Glu Lys Ala Leu Gln Gly Glu Asp Val Arg Thr Ala Asn Val
305 310 315 320
Ile Ala Ala Glu Ala Val Thr Cys Leu Val Ile Asp Arg Asp Ser Phe
325 330 335
Lys His Leu Ile Gly Gly Leu Asp Asp Val Ser Asn Lys Ala Tyr Glu
340 345 350
Asp Ala Glu Ala Lys Ala Lys Tyr Glu Ala Glu Ala Ala Phe Phe Ala
355 360 365
Asn Leu Lys Leu Ser Asp Phe Asn Ile Ile Asp Thr Leu Gly Val Gly
370 375 380
Gly Phe Gly Arg Val Glu Leu Val Gln Leu Lys Ser Glu Glu Ser Lys
385 390 395 400
Thr Phe Ala Met Lys Ile Leu Lys Lys Arg His Ile Val Asp Thr Arg
405 410 415
Gln Gln Glu His Ile Arg Ser Glu Lys Gln Ile Met Gln Gly Ala His
420 425 430
Ser Asp Phe Ile Val Arg Leu Tyr Arg Thr Phe Lys Asp Ser Lys Tyr
435 440 445
Leu Tyr Met Leu Met Glu Ala Cys Leu Gly Gly Glu Leu Trp Thr Ile
450 455 460
Leu Arg Asp Arg Gly Ser Phe Glu Asp Ser Thr Thr Arg Phe Tyr Thr
465 470 475 480
Ala Cys Val Val Glu Ala Phe Ala Tyr Leu His Ser Lys Gly Ile Ile
485 490 495
Tyr Arg Asp Leu Lys Pro Glu Asn Leu Ile Leu Asp His Arg Gly Tyr
500 505 510
Ala Lys Leu Val Asp Phe Gly Phe Ala Lys Lys Ile Gly Phe Gly Lys
515 520 525
Lys Thr Trp Thr Phe Cys Gly Thr Pro Glu Tyr Val Ala Pro Glu Ile
530 535 540
Ile Leu Asn Lys Gly His Asp Ile Ser Ala Asp Tyr Trp Ser Leu Gly
545 550 555 560
Ile Leu Met Tyr Glu Leu Leu Thr Gly Ser Pro Pro Phe Ser Gly Pro
565 570 575
Asp Pro Met Lys Thr Tyr Asn Ile Ile Leu Arg Gly Ile Asp Met Ile
580 585 590
Glu Phe Pro Lys Lys Ile Ala Lys Asn Ala Ala Asn Leu Ile Lys Lys
595 600 605
Leu Cys Arg Asp Asn Pro Ser Glu Arg Leu Gly Asn Leu Lys Asn Gly
610 615 620
Val Lys Asp Ile Gln Lys His Lys Trp Phe Glu Gly Phe Asn Trp Glu
625 630 635 640
Gly Leu Arg Lys Gly Thr Leu Thr Pro Pro Ile Ile Pro Ser Val Ala
645 650 655
Ser Pro Thr Asp Thr Ser Asn Phe Asp Ser Phe Pro Glu Asp Asn Asp
660 665 670
Glu Pro Pro Pro Asp Asp Asn Ser Gly Trp Asp Ile Asp Phe Ser Asp
675 680 685
Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
690 695 700
Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
705 710 715 720
Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
725 730 735
Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro

740 745 750
Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
755 760 765
Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
770 775 780
Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
785 790 795 800
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
805 810 815
Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
820 825 830
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
835 840 845
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
850 855 860
Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
865 870 875 880
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
885 890 895
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
900 905 910
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
915 920 925
Glu Leu Tyr Lys
930

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2184 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2181
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC 720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

GGA CTC AGA TCT CGA GGC ACC ATG AGC GAC GTG GCT ATT GTG AAG GAG 768
Gly Leu Arg Ser Arg Gly Thr Met Ser Asp Val Ala Ile Val Lys Glu
245 250 255

GGT TGG CTG CAC AAA CGA GGG GAG TAC ATC AAG ACC TGG CGG CCA CGC 816
Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg
260 265 270

TAC TTC CTC CTC AAG AAT GAT GGC ACC TTC ATT GGC TAC AAG GAG CGG 864
Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg
275 280 285

CCG CAG GAT GTG GAC CAA CGT GAG GCT CCC CTC AAC AAC TTC TCT GTG 912

Pro Gln Asp Val Asp Gln Arg Glu Ala Pro Leu Asn Asn Phe Ser Val
    290   295   300

GCG CAG TGC CAG CTG ATG AAG ACG GAG CGG CCC CGG CCC AAC ACC TTC   960
Ala Gln Cys Gln Leu Met Lys Thr Glu Arg Pro Arg Pro Asn Thr Phe
305   310   315   320

ATC ATC CGC TGC CTG CAG TGG ACC ACT GTC ATC GAA CGC ACC TTC CAT   1008
Ile Ile Arg Cys Leu Gln Trp Thr Thr Val Ile Glu Arg Thr Phe His
                325   330   335

GTG GAG ACT CCT GAG GAG CGG GAG GAG TGG ACA ACC GCC ATC CAG ACT   1056
Val Glu Thr Pro Glu Glu Arg Glu Glu Trp Thr Thr Ala Ile Gln Thr
            340   345   350

GTG GCT GAC GGC CTC AAG AAG CAG GAG GAG GAG GAG ATG GAC TTC CGG   1104
Val Ala Asp Gly Leu Lys Lys Gln Glu Glu Glu Glu Met Asp Phe Arg
        355   360   365

TCG GGC TCA CCC AGT GAC AAC TCA GGG GCT GAA GAG ATG GAG GTG TCC   1152
Ser Gly Ser Pro Ser Asp Asn Ser Gly Ala Glu Glu Met Glu Val Ser
    370   375   380

CTG GCC AAG CCC AAG CAC CGC GTG ACC ATG AAC GAG TTT GAG TAC CTG   1200
Leu Ala Lys Pro Lys His Arg Val Thr Met Asn Glu Phe Glu Tyr Leu
385   390   395   400

AAG CTG CTG GGC AAG GGC ACT TTC GGC AAG GTG ATC CTG GTG AAG GAG   1248
Lys Leu Leu Gly Lys Gly Thr Phe Gly Lys Val Ile Leu Val Lys Glu
                405   410   415

AAG GCC ACA GGC CGC TAC TAC GCC ATG AAG ATC CTC AAG AAG GAA GTC   1296
Lys Ala Thr Gly Arg Tyr Tyr Ala Met Lys Ile Leu Lys Lys Glu Val
            420   425   430

ATC GTG GCC AAG GAC GAG GTG GCC CAC ACA CTC ACC GAG AAC CGC GTC   1344
Ile Val Ala Lys Asp Glu Val Ala His Thr Leu Thr Glu Asn Arg Val
        435   440   445

CTG CAG AAC TCC AGG CAC CCC TTC CTC ACA GCC CTG AAG TAC TCT TTC   1392
Leu Gln Asn Ser Arg His Pro Phe Leu Thr Ala Leu Lys Tyr Ser Phe
    450   455   460

CAG ACC CAC GAC CGC CTC TGC TTT GTC ATG GAG TAC GCC AAC GGG GGC   1440
Gln Thr His Asp Arg Leu Cys Phe Val Met Glu Tyr Ala Asn Gly Gly
465   470   475   480

GAG CTG TTC TTC CAC CTG TCC CGG GAA CGT GTG TTC TCC GAG GAC CGG   1488
Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp Arg
                485   490   495

GCC CGC TTC TAT GGC GCT GAG ATT GTG TCA GCC CTG GAC TAC CTG CAC   1536
Ala Arg Phe Tyr Gly Ala Glu Ile Val Ser Ala Leu Asp Tyr Leu His
            500   505   510

TCG GAG AAG AAC GTG GTG TAC CGG GAC CTC AAG CTG GAG AAC CTC ATG   1584
Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Met
        515   520   525

CTG GAC AAG GAC GGG CAC ATT AAG ATC ACA GAC TTC GGG CTG TGC AAG 1632
Leu Asp Lys Asp Gly His Ile Lys Ile Thr Asp Phe Gly Leu Cys Lys
530 535 540

GAG GGG ATC AAG GAC GGT GCC ACC ATG AAG ACC TTT TGC GGC ACA CCT 1680
Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr Pro
545 550 555 560

GAG TAC CTG GCC CCC GAG GTG CTG GAG GAC AAT GAC TAC GGC CGT GCA 1728
Glu Tyr Leu Ala Pro Glu Val Leu Glu Asp Asn Asp Tyr Gly Arg Ala
565 570 575

GTG GAC TGG TGG GGG CTG GGC GTG GTC ATG TAC GAG ATG ATG TGC GGT 1776
Val Asp Trp Trp Gly Leu Gly Val Val Met Tyr Glu Met Met Cys Gly
580 585 590

CGC CTG CCC TTC TAC AAC CAG GAC CAT GAG AAG CTT TTT GAG CTC ATC 1824
Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu Ile
595 600 605

CTC ATG GAG GAG ATC CGC TTC CCG CGC ACG CTT GGT CCC GAG GCC AAG 1872
Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala Lys
610 615 620

TCC TTG CTT TCA GGG CTG CTC AAG AAG GAC CCC AAG CAG AGG CTT GGC 1920
Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu Gly
625 630 635 640

GGG GGC TCC GAG GAC GCC AAG GAG ATC ATG CAG CAT CGC TTC TTT GCC 1968
Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Ala
645 650 655

GGT ATC GTG TGG CAG CAC GTG TAC GAG AAG AAG CTC AGC CCA CCC TTC 2016
Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro Phe
660 665 670

AAG CCC CAG GTC ACG TCG GAG ACT GAC ACC AGG TAT TTT GAT GAG GAG 2064
Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu Glu
675 680 685

TTC ACG GCC CAG ATG ATC ACC ATC ACA CCA CCT GAC CAA GAT GAC AGC 2112
Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp Ser
690 695 700

ATG GAG TGT GTG GAC AGC GAG CGC AGG CCC CAC TTC CCC CAG TTC TCC 2160
Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe Ser
705 710 715 720

TAC TCG GCC AGC AGC ACG GCC TGA 2184
Tyr Ser Ala Ser Ser Thr Ala
725

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 727 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

```
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1              5                   10                  15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240
Gly Leu Arg Ser Arg Gly Thr Met Ser Asp Val Ala Ile Val Lys Glu
                245                 250                 255
Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg
            260                 265                 270
Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg
        275                 280                 285
Pro Gln Asp Val Asp Gln Arg Glu Ala Pro Leu Asn Asn Phe Ser Val
    290                 295                 300
Ala Gln Cys Gln Leu Met Lys Thr Glu Arg Pro Arg Pro Asn Thr Phe
305                 310                 315                 320
Ile Ile Arg Cys Leu Gln Trp Thr Thr Val Ile Glu Arg Thr Phe His
                325                 330                 335
Val Glu Thr Pro Glu Glu Arg Glu Glu Trp Thr Thr Ala Ile Gln Thr
            340                 345                 350
Val Ala Asp Gly Leu Lys Lys Gln Glu Glu Glu Glu Met Asp Phe Arg
        355                 360                 365
Ser Gly Ser Pro Ser Asp Asn Ser Gly Ala Glu Glu Met Glu Val Ser
    370                 375                 380
Leu Ala Lys Pro Lys His Arg Val Thr Met Asn Glu Phe Glu Tyr Leu
```

385 390 395 400
Lys Leu Leu Gly Lys Gly Thr Phe Gly Lys Val Ile Leu Val Lys Glu
405 410 415
Lys Ala Thr Gly Arg Tyr Tyr Ala Met Lys Ile Leu Lys Lys Glu Val
420 425 430
Ile Val Ala Lys Asp Glu Val Ala His Thr Leu Thr Glu Asn Arg Val
435 440 445
Leu Gln Asn Ser Arg His Pro Phe Leu Thr Ala Leu Lys Tyr Ser Phe
450 455 460
Gln Thr His Asp Arg Leu Cys Phe Val Met Glu Tyr Ala Asn Gly Gly
465 470 475 480
Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp Arg
485 490 495
Ala Arg Phe Tyr Gly Ala Glu Ile Val Ser Ala Leu Asp Tyr Leu His
500 505 510
Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Met
515 520 525
Leu Asp Lys Asp Gly His Ile Lys Ile Thr Asp Phe Gly Leu Cys Lys
530 535 540
Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr Pro
545 550 555 560
Glu Tyr Leu Ala Pro Glu Val Leu Glu Asp Asn Asp Tyr Gly Arg Ala
565 570 575
Val Asp Trp Trp Gly Leu Gly Val Val Met Tyr Glu Met Met Cys Gly
580 585 590
Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu Ile
595 600 605
Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala Lys
610 615 620
Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu Gly
625 630 635 640
Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Ala
645 650 655
Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro Phe
660 665 670
Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu Glu
675 680 685
Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp Ser
690 695 700
Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe Ser
705 710 715 720
Tyr Ser Ala Ser Ser Thr Ala
725

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2394 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2391
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

ATG GAC GAA CTG TTC CCC CTC ATC TTC CCG GCA GAG CCA GCC CAG GCC 48
Met Asp Glu Leu Phe Pro Leu Ile Phe Pro Ala Glu Pro Ala Gln Ala
1 5 10 15

TCT GGC CCC TAT GTG GAG ATC ATT GAG CAG CCC AAG CAG CGG GGC ATG 96
Ser Gly Pro Tyr Val Glu Ile Ile Glu Gln Pro Lys Gln Arg Gly Met
20 25 30

CGC TTC CGC TAC AAG TGC GAG GGG CGC TCC GCG GGC AGC ATC CCA GGC 144
Arg Phe Arg Tyr Lys Cys Glu Gly Arg Ser Ala Gly Ser Ile Pro Gly
35 40 45

GAG AGG AGC ACA GAT ACC ACC AAG ACC CAC CCC ACC ATC AAG ATC AAT 192
Glu Arg Ser Thr Asp Thr Thr Lys Thr His Pro Thr Ile Lys Ile Asn
50 55 60

GGC TAC ACA GGA CCA GGG ACA GTG CGC ATC TCC CTG GTC ACC AAG GAC 240
Gly Tyr Thr Gly Pro Gly Thr Val Arg Ile Ser Leu Val Thr Lys Asp
65 70 75 80

CCT CCT CAC CGG CCT CAC CCC CAC GAG CTT GTA GGA AAG GAC TGC CGG 288
Pro Pro His Arg Pro His Pro His Glu Leu Val Gly Lys Asp Cys Arg
85 90 95

GAT GGC TTC TAT GAG GCT GAG CTC TGC CCG GAC CGC TGC ATC CAC AGT 336
Asp Gly Phe Tyr Glu Ala Glu Leu Cys Pro Asp Arg Cys Ile His Ser
100 105 110

TTC CAG AAC CTG GGA ATC CAG TGT GTG AAG AAG CGG GAC CTG GAG CAG 384
Phe Gln Asn Leu Gly Ile Gln Cys Val Lys Lys Arg Asp Leu Glu Gln
115 120 125

GCT ATC AGT CAG CGC ATC CAG ACC AAC AAC AAC CCC TTC CAA GTT CCT 432
Ala Ile Ser Gln Arg Ile Gln Thr Asn Asn Asn Pro Phe Gln Val Pro
130 135 140

ATA GAA GAG CAG CGT GGG GAC TAC GAC CTG AAT GCT GTG CGG CTC TGC 480
Ile Glu Glu Gln Arg Gly Asp Tyr Asp Leu Asn Ala Val Arg Leu Cys
145 150 155 160

TTC CAG GTG ACA GTG CGG GAC CCA TCA GGC AGG CCC CTC CGC CTG CCG 528
Phe Gln Val Thr Val Arg Asp Pro Ser Gly Arg Pro Leu Arg Leu Pro
165 170 175

CCT GTC CTT CCT CAT CCC ATC TTT GAC AAT CGT GCC CCC AAC ACT GCC 576
Pro Val Leu Pro His Pro Ile Phe Asp Asn Arg Ala Pro Asn Thr Ala
180 185 190

GAG CTC AAG ATC TGC CGA GTG AAC CGA AAC TCT GGC AGC TGC CTC GGT 624
Glu Leu Lys Ile Cys Arg Val Asn Arg Asn Ser Gly Ser Cys Leu Gly
195 200 205

GGG GAT GAG ATC TTC CTA CTG TGT GAC AAG GTG CAG AAA GAG GAC ATT 672
Gly Asp Glu Ile Phe Leu Leu Cys Asp Lys Val Gln Lys Glu Asp Ile
210 215 220

GAG GTG TAT TTC ACG GGA CCA GGC TGG GAG GCC CGA GGC TCC TTT TCG 720
Glu Val Tyr Phe Thr Gly Pro Gly Trp Glu Ala Arg Gly Ser Phe Ser
225 230 235 240

CAA GCT GAT GTG CAC CGA CAA GTG GCC ATT GTG TTC CGG ACC CCT CCC 768
Gln Ala Asp Val His Arg Gln Val Ala Ile Val Phe Arg Thr Pro Pro
245 250 255

TAC GCA GAC CCC AGC CTG CAG GCT CCT GTG CGT GTC TCC ATG CAG CTG 816
Tyr Ala Asp Pro Ser Leu Gln Ala Pro Val Arg Val Ser Met Gln Leu
260 265 270

CGG CGG CCT TCC GAC CGG GAG CTC AGT GAG CCC ATG GAA TTC CAG TAC 864
Arg Arg Pro Ser Asp Arg Glu Leu Ser Glu Pro Met Glu Phe Gln Tyr
275 280 285

CTG CCA GAT ACA GAC GAT CGT CAC CGG ATT GAG GAG AAA CGT AAA AGG 912
Leu Pro Asp Thr Asp Asp Arg His Arg Ile Glu Glu Lys Arg Lys Arg
290 295 300

ACA TAT GAG ACC TTC AAG AGC ATC ATG AAG AAG AGT CCT TTC AGC GGA 960
Thr Tyr Glu Thr Phe Lys Ser Ile Met Lys Lys Ser Pro Phe Ser Gly
305 310 315 320

CCC ACC GAC CCC CGG CCT CCA CCT CGA CGC ATT GCT GTG CCT TCC CGC 1008
Pro Thr Asp Pro Arg Pro Pro Pro Arg Arg Ile Ala Val Pro Ser Arg
325 330 335

AGC TCA GCT TCT GTC CCC AAG CCA GCA CCC CAG CCC TAT CCC TTT ACG 1056
Ser Ser Ala Ser Val Pro Lys Pro Ala Pro Gln Pro Tyr Pro Phe Thr
340 345 350

TCA TCC CTG AGC ACC ATC AAC TAT GAT GAG TTT CCC ACC ATG GTG TTT 1104
Ser Ser Leu Ser Thr Ile Asn Tyr Asp Glu Phe Pro Thr Met Val Phe
355 360 365

CCT TCT GGG CAG ATC AGC CAG GCC TCG GCC TTG GCC CCG GCC CCT CCC 1152
Pro Ser Gly Gln Ile Ser Gln Ala Ser Ala Leu Ala Pro Ala Pro Pro
370 375 380

CAA GTC CTG CCC CAG GCT CCA GCC CCT GCC CCT GCT CCA GCC ATG GTA 1200
Gln Val Leu Pro Gln Ala Pro Ala Pro Ala Pro Ala Pro Ala Met Val
385 390 395 400

TCA GCT CTG GCC CAG GCC CCA GCC CCT GTC CCA GTC CTA GCC CCA GGC 1248
Ser Ala Leu Ala Gln Ala Pro Ala Pro Val Pro Val Leu Ala Pro Gly
405 410 415

CCT CCT CAG GCT GTG GCC CCA CCT GCC CCC AAG CCC ACC CAG GCT GGG 1296
Pro Pro Gln Ala Val Ala Pro Pro Ala Pro Lys Pro Thr Gln Ala Gly
420 425 430

GAA GGA ACG CTG TCA GAG GCC CTG CTG CAG CTG CAG TTT GAT GAT GAA 1344
Glu Gly Thr Leu Ser Glu Ala Leu Leu Gln Leu Gln Phe Asp Asp Glu
435 440 445

GAC CTG GGG GCC TTG CTT GGC AAC AGC ACA GAC CCA GCT GTG TTC ACA 1392

Asp Leu Gly Ala Leu Leu Gly Asn Ser Thr Asp Pro Ala Val Phe Thr
450 455 460

GAC CTG GCA TCC GTC GAC AAC TCC GAG TTT CAG CAG CTG CTG AAC CAG 1440
Asp Leu Ala Ser Val Asp Asn Ser Glu Phe Gln Gln Leu Leu Asn Gln
465 470 475 480

GGC ATA CCT GTG GCC CCC CAC ACA ACT GAG CCC ATG CTG ATG GAG TAC 1488
Gly Ile Pro Val Ala Pro His Thr Thr Glu Pro Met Leu Met Glu Tyr
485 490 495

CCT GAG GCT ATA ACT CGC CTA GTG ACA GGG GCC CAG AGG CCC CCC GAC 1536
Pro Glu Ala Ile Thr Arg Leu Val Thr Gly Ala Gln Arg Pro Pro Asp
500 505 510

CCA GCT CCT GCT CCA CTG GGG GCC CCG GGG CTC CCC AAT GGC CTC CTT 1584
Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
515 520 525

TCA GGA GAT GAA GAC TTC TCC TCC ATT GCG GAC ATG GAC TTC TCA GCC 1632
Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
530 535 540

CTG CTG AGT CAG ATC AGC TCC TTG GAT CCA CCG GTC GCC ACC ATG GTG 1680
Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
545 550 555 560

AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG 1728
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
565 570 575

CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC 1776
Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
580 585 590

GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC 1824
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
595 600 605

ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC 1872
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
610 615 620

TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC 1920
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
625 630 635 640

GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC 1968
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
645 650 655

ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG 2016
Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
660 665 670

TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC 2064
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
675 680 685

```
TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC      2112
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
    690                 695                 700

AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC      2160
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
705                 710                 715                 720

AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG      2208
Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                725                 730                 735

CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG      2256
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
            740                 745                 750

CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA      2304
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
        755                 760                 765

GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC      2352
Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
    770                 775                 780

GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA               2394
Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785                 790                 795
```

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 797 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

```
Met Asp Glu Leu Phe Pro Leu Ile Phe Pro Ala Glu Pro Ala Gln Ala
 1               5                  10                  15
Ser Gly Pro Tyr Val Glu Ile Ile Glu Gln Pro Lys Gln Arg Gly Met
            20                  25                  30
Arg Phe Arg Tyr Lys Cys Glu Gly Arg Ser Ala Gly Ser Ile Pro Gly
        35                  40                  45
Glu Arg Ser Thr Asp Thr Thr Lys Thr His Pro Thr Ile Lys Ile Asn
    50                  55                  60
Gly Tyr Thr Gly Pro Gly Thr Val Arg Ile Ser Leu Val Thr Lys Asp
65                  70                  75                  80
Pro Pro His Arg Pro His Pro His Glu Leu Val Gly Lys Asp Cys Arg
                85                  90                  95
Asp Gly Phe Tyr Glu Ala Glu Leu Cys Pro Asp Arg Cys Ile His Ser
            100                 105                 110
Phe Gln Asn Leu Gly Ile Gln Cys Val Lys Lys Arg Asp Leu Glu Gln
```

115 120 125
Ala Ile Ser Gln Arg Ile Gln Thr Asn Asn Asn Pro Phe Gln Val Pro
130 135 140
Ile Glu Glu Gln Arg Gly Asp Tyr Asp Leu Asn Ala Val Arg Leu Cys
145 150 155 160
Phe Gln Val Thr Val Arg Asp Pro Ser Gly Arg Pro Leu Arg Leu Pro
165 170 175
Pro Val Leu Pro His Pro Ile Phe Asp Asn Arg Ala Pro Asn Thr Ala
180 185 190
Glu Leu Lys Ile Cys Arg Val Asn Arg Asn Ser Gly Ser Cys Leu Gly
195 200 205
Gly Asp Glu Ile Phe Leu Leu Cys Asp Lys Val Gln Lys Glu Asp Ile
210 215 220
Glu Val Tyr Phe Thr Gly Pro Gly Trp Glu Ala Arg Gly Ser Phe Ser
225 230 235 240
Gln Ala Asp Val His Arg Gln Val Ala Ile Val Phe Arg Thr Pro Pro
245 250 255
Tyr Ala Asp Pro Ser Leu Gln Ala Pro Val Arg Val Ser Met Gln Leu
260 265 270
Arg Arg Pro Ser Asp Arg Glu Leu Ser Glu Pro Met Glu Phe Gln Tyr
275 280 285
Leu Pro Asp Thr Asp Asp Arg His Arg Ile Glu Glu Lys Arg Lys Arg
290 295 300
Thr Tyr Glu Thr Phe Lys Ser Ile Met Lys Lys Ser Pro Phe Ser Gly
305 310 315 320
Pro Thr Asp Pro Arg Pro Pro Pro Arg Arg Ile Ala Val Pro Ser Arg
325 330 335
Ser Ser Ala Ser Val Pro Lys Pro Ala Pro Gln Pro Tyr Pro Phe Thr
340 345 350
Ser Ser Leu Ser Thr Ile Asn Tyr Asp Glu Phe Pro Thr Met Val Phe
355 360 365
Pro Ser Gly Gln Ile Ser Gln Ala Ser Ala Leu Ala Pro Ala Pro Pro
370 375 380
Gln Val Leu Pro Gln Ala Pro Ala Pro Ala Pro Ala Pro Ala Met Val
385 390 395 400
Ser Ala Leu Ala Gln Ala Pro Ala Pro Val Pro Val Leu Ala Pro Gly
405 410 415
Pro Pro Gln Ala Val Ala Pro Pro Ala Pro Lys Pro Thr Gln Ala Gly
420 425 430
Glu Gly Thr Leu Ser Glu Ala Leu Leu Gln Leu Gln Phe Asp Asp Glu
435 440 445
Asp Leu Gly Ala Leu Leu Gly Asn Ser Thr Asp Pro Ala Val Phe Thr
450 455 460
Asp Leu Ala Ser Val Asp Asn Ser Glu Phe Gln Gln Leu Leu Asn Gln
465 470 475 480
Gly Ile Pro Val Ala Pro His Thr Thr Glu Pro Met Leu Met Glu Tyr
485 490 495
Pro Glu Ala Ile Thr Arg Leu Val Thr Gly Ala Gln Arg Pro Pro Asp
500 505 510
Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
515 520 525
Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
530 535 540
Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
545 550 555 560
Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
565 570 575
Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly

```
            580                 585                 590
Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
        595                 600                 605
Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
    610                 615                 620
Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
625                 630                 635                 640
Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
                645                 650                 655
Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
            660                 665                 670
Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
        675                 680                 685
Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
    690                 695                 700
Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
705                 710                 715                 720
Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                725                 730                 735
Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
            740                 745                 750
Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
        755                 760                 765
Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
    770                 775                 780
Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785                 790                 795
```

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2394 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2391
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

```
ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTC CCC ATC CTG      48
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
 1               5                  10                  15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC      96
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
            20                  25                  30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC     144
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
        35                  40                  45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC     192
```

```
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
    50                  55                  60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG      240
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65                  70                  75                  80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG      288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                85                  90                  95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG      336
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
            100                 105                 110

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC      384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
        115                 120                 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC      432
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
    130                 135                 140

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC      480
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145                 150                 155                 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC      528
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                165                 170                 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC      576
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
            180                 185                 190

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG      624
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
        195                 200                 205

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC      672
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
    210                 215                 220

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC      720
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225                 230                 235                 240

GGA CTC AGA TCT CGA GCC ATG GAC GAA CTG TTC CCC CTC ATC TTC CCG      768
Gly Leu Arg Ser Arg Ala Met Asp Glu Leu Phe Pro Leu Ile Phe Pro
                245                 250                 255

GCA GAG CCA GCC CAG GCC TCT GGC CCC TAT GTG GAG ATC ATT GAG CAG      816
Ala Glu Pro Ala Gln Ala Ser Gly Pro Tyr Val Glu Ile Ile Glu Gln
            260                 265                 270

CCC AAG CAG CGG GGC ATG CGC TTC CGC TAC AAG TGC GAG GGG CGC TCC      864
Pro Lys Gln Arg Gly Met Arg Phe Arg Tyr Lys Cys Glu Gly Arg Ser
        275                 280                 285
```

GCG GGC AGC ATC CCA GGC GAG AGG AGC ACA GAT ACC ACC AAG ACC CAC 912
Ala Gly Ser Ile Pro Gly Glu Arg Ser Thr Asp Thr Thr Lys Thr His
290 295 300

CCC ACC ATC AAG ATC AAT GGC TAC ACA GGA CCA GGG ACA GTG CGC ATC 960
Pro Thr Ile Lys Ile Asn Gly Tyr Thr Gly Pro Gly Thr Val Arg Ile
305 310 315 320

TCC CTG GTC ACC AAG GAC CCT CCT CAC CGG CCT CAC CCC CAC GAG CTT 1008
Ser Leu Val Thr Lys Asp Pro Pro His Arg Pro His Pro His Glu Leu
325 330 335

GTA GGA AAG GAC TGC CGG GAT GGC TTC TAT GAG GCT GAG CTC TGC CCG 1056
Val Gly Lys Asp Cys Arg Asp Gly Phe Tyr Glu Ala Glu Leu Cys Pro
340 345 350

GAC CGC TGC ATC CAC AGT TTC CAG AAC CTG GGA ATC CAG TGT GTG AAG 1104
Asp Arg Cys Ile His Ser Phe Gln Asn Leu Gly Ile Gln Cys Val Lys
355 360 365

AAG CGG GAC CTG GAG CAG GCT ATC AGT CAG CGC ATC CAG ACC AAC AAC 1152
Lys Arg Asp Leu Glu Gln Ala Ile Ser Gln Arg Ile Gln Thr Asn Asn
370 375 380

AAC CCC TTC CAA GTT CCT ATA GAA GAG CAG CGT GGG GAC TAC GAC CTG 1200
Asn Pro Phe Gln Val Pro Ile Glu Glu Gln Arg Gly Asp Tyr Asp Leu
385 390 395 400

AAT GCT GTG CGG CTC TGC TTC CAG GTG ACA GTG CGG GAC CCA TCA GGC 1248
Asn Ala Val Arg Leu Cys Phe Gln Val Thr Val Arg Asp Pro Ser Gly
405 410 415

AGG CCC CTC CGC CTG CCG CCT GTC CTT CCT CAT CCC ATC TTT GAC AAT 1296
Arg Pro Leu Arg Leu Pro Pro Val Leu Pro His Pro Ile Phe Asp Asn
420 425 430

CGT GCC CCC AAC ACT GCC GAG CTC AAG ATC TGC CGA GTG AAC CGA AAC 1344
Arg Ala Pro Asn Thr Ala Glu Leu Lys Ile Cys Arg Val Asn Arg Asn
435 440 445

TCT GGC AGC TGC CTC GGT GGG GAT GAG ATC TTC CTA CTG TGT GAC AAG 1392
Ser Gly Ser Cys Leu Gly Gly Asp Glu Ile Phe Leu Leu Cys Asp Lys
450 455 460

GTG CAG AAA GAG GAC ATT GAG GTG TAT TTC ACG GGA CCA GGC TGG GAG 1440
Val Gln Lys Glu Asp Ile Glu Val Tyr Phe Thr Gly Pro Gly Trp Glu
465 470 475 480

GCC CGA GGC TCC TTT TCG CAA GCT GAT GTG CAC CGA CAA GTG GCC ATT 1488
Ala Arg Gly Ser Phe Ser Gln Ala Asp Val His Arg Gln Val Ala Ile
485 490 495

GTG TTC CGG ACC CCT CCC TAC GCA GAC CCC AGC CTG CAG GCT CCT GTG 1536
Val Phe Arg Thr Pro Pro Tyr Ala Asp Pro Ser Leu Gln Ala Pro Val
500 505 510

CGT GTC TCC ATG CAG CTG CGG CGG CCT TCC GAC CGG GAG CTC AGT GAG 1584

Arg Val Ser Met Gln Leu Arg Arg Pro Ser Asp Arg Glu Leu Ser Glu
515 520 525

CCC ATG GAA TTC CAG TAC CTG CCA GAT ACA GAC GAT CGT CAC CGG ATT 1632
Pro Met Glu Phe Gln Tyr Leu Pro Asp Thr Asp Asp Arg His Arg Ile
530 535 540

GAG GAG AAA CGT AAA AGG ACA TAT GAG ACC TTC AAG AGC ATC ATG AAG 1680
Glu Glu Lys Arg Lys Arg Thr Tyr Glu Thr Phe Lys Ser Ile Met Lys
545 550 555 560

AAG AGT CCT TTC AGC GGA CCC ACC GAC CCC CGG CCT CCA CCT CGA CGC 1728
Lys Ser Pro Phe Ser Gly Pro Thr Asp Pro Arg Pro Pro Pro Arg Arg
565 570 575

ATT GCT GTG CCT TCC CGC AGC TCA GCT TCT GTC CCC AAG CCA GCA CCC 1776
Ile Ala Val Pro Ser Arg Ser Ser Ala Ser Val Pro Lys Pro Ala Pro
580 585 590

CAG CCC TAT CCC TTT ACG TCA TCC CTG AGC ACC ATC AAC TAT GAT GAG 1824
Gln Pro Tyr Pro Phe Thr Ser Ser Leu Ser Thr Ile Asn Tyr Asp Glu
595 600 605

TTT CCC ACC ATG GTG TTT CCT TCT GGG CAG ATC AGC CAG GCC TCG GCC 1872
Phe Pro Thr Met Val Phe Pro Ser Gly Gln Ile Ser Gln Ala Ser Ala
610 615 620

TTG GCC CCG GCC CCT CCC CAA GTC CTG CCC CAG GCT CCA GCC CCT GCC 1920
Leu Ala Pro Ala Pro Pro Gln Val Leu Pro Gln Ala Pro Ala Pro Ala
625 630 635 640

CCT GCT CCA GCC ATG GTA TCA GCT CTG GCC CAG GCC CCA GCC CCT GTC 1968
Pro Ala Pro Ala Met Val Ser Ala Leu Ala Gln Ala Pro Ala Pro Val
645 650 655

CCA GTC CTA GCC CCA GGC CCT CCT CAG GCT GTG GCC CCA CCT GCC CCC 2016
Pro Val Leu Ala Pro Gly Pro Pro Gln Ala Val Ala Pro Pro Ala Pro
660 665 670

AAG CCC ACC CAG GCT GGG GAA GGA ACG CTG TCA GAG GCC CTG CTG CAG 2064
Lys Pro Thr Gln Ala Gly Glu Gly Thr Leu Ser Glu Ala Leu Leu Gln
675 680 685

CTG CAG TTT GAT GAT GAA GAC CTG GGG GCC TTG CTT GGC AAC AGC ACA 2112
Leu Gln Phe Asp Asp Glu Asp Leu Gly Ala Leu Leu Gly Asn Ser Thr
690 695 700

GAC CCA GCT GTG TTC ACA GAC CTG GCA TCC GTC GAC AAC TCC GAG TTT 2160
Asp Pro Ala Val Phe Thr Asp Leu Ala Ser Val Asp Asn Ser Glu Phe
705 710 715 720

CAG CAG CTG CTG AAC CAG GGC ATA CCT GTG GCC CCC CAC ACA ACT GAG 2208
Gln Gln Leu Leu Asn Gln Gly Ile Pro Val Ala Pro His Thr Thr Glu
725 730 735

CCC ATG CTG ATG GAG TAC CCT GAG GCT ATA ACT CGC CTA GTG ACA GGG 2256
Pro Met Leu Met Glu Tyr Pro Glu Ala Ile Thr Arg Leu Val Thr Gly
740 745 750

GCC CAG AGG CCC CCC GAC CCA GCT CCT GCT CCA CTG GGG GCC CCG GGG 2304
Ala Gln Arg Pro Pro Asp Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly
755 760 765

CTC CCC AAT GGC CTC CTT TCA GGA GAT GAA GAC TTC TCC TCC ATT GCG 2352
Leu Pro Asn Gly Leu Leu Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala
770 775 780

GAC ATG GAC TTC TCA GCC CTG CTG AGT CAG ATC AGC TCC TAA 2394
Asp Met Asp Phe Ser Ala Leu Leu Ser Gln Ile Ser Ser
785 790 795

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 797 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
1 5 10 15
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 55 60
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
65 70 75 80
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85 90 95
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
100 105 110
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
130 135 140
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
145 150 155 160
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
195 200 205
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
210 215 220
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240
Gly Leu Arg Ser Arg Ala Met Asp Glu Leu Phe Pro Leu Ile Phe Pro

```
                245                 250                 255
Ala Glu Pro Ala Gln Ala Ser Gly Pro Tyr Val Glu Ile Ile Glu Gln
            260                 265                 270
Pro Lys Gln Arg Gly Met Arg Phe Arg Tyr Lys Cys Glu Gly Arg Ser
        275                 280                 285
Ala Gly Ser Ile Pro Gly Glu Arg Ser Thr Asp Thr Thr Lys Thr His
    290                 295                 300
Pro Thr Ile Lys Ile Asn Gly Tyr Thr Gly Pro Gly Thr Val Arg Ile
305                 310                 315                 320
Ser Leu Val Thr Lys Asp Pro Pro His Arg Pro His Pro His Glu Leu
                325                 330                 335
Val Gly Lys Asp Cys Arg Asp Gly Phe Tyr Glu Ala Glu Leu Cys Pro
            340                 345                 350
Asp Arg Cys Ile His Ser Phe Gln Asn Leu Gly Ile Gln Cys Val Lys
        355                 360                 365
Lys Arg Asp Leu Glu Gln Ala Ile Ser Gln Arg Ile Gln Thr Asn Asn
    370                 375                 380
Asn Pro Phe Gln Val Pro Ile Glu Glu Gln Arg Gly Asp Tyr Asp Leu
385                 390                 395                 400
Asn Ala Val Arg Leu Cys Phe Gln Val Thr Val Arg Asp Pro Ser Gly
                405                 410                 415
Arg Pro Leu Arg Leu Pro Pro Val Leu Pro His Pro Ile Phe Asp Asn
            420                 425                 430
Arg Ala Pro Asn Thr Ala Glu Leu Lys Ile Cys Arg Val Asn Arg Asn
        435                 440                 445
Ser Gly Ser Cys Leu Gly Gly Asp Glu Ile Phe Leu Leu Cys Asp Lys
    450                 455                 460
Val Gln Lys Glu Asp Ile Glu Val Tyr Phe Thr Gly Pro Gly Trp Glu
465                 470                 475                 480
Ala Arg Gly Ser Phe Ser Gln Ala Asp Val His Arg Gln Val Ala Ile
                485                 490                 495
Val Phe Arg Thr Pro Pro Tyr Ala Asp Pro Ser Leu Gln Ala Pro Val
            500                 505                 510
Arg Val Ser Met Gln Leu Arg Arg Pro Ser Asp Arg Glu Leu Ser Glu
        515                 520                 525
Pro Met Glu Phe Gln Tyr Leu Pro Asp Thr Asp Asp Arg His Arg Ile
    530                 535                 540
Glu Glu Lys Arg Lys Arg Thr Tyr Glu Thr Phe Lys Ser Ile Met Lys
545                 550                 555                 560
Lys Ser Pro Phe Ser Gly Pro Thr Asp Pro Arg Pro Pro Pro Arg Arg
                565                 570                 575
Ile Ala Val Pro Ser Arg Ser Ser Ala Ser Val Pro Lys Pro Ala Pro
            580                 585                 590
Gln Pro Tyr Pro Phe Thr Ser Ser Leu Ser Thr Ile Asn Tyr Asp Glu
        595                 600                 605
Phe Pro Thr Met Val Phe Pro Ser Gly Gln Ile Ser Gln Ala Ser Ala
    610                 615                 620
Leu Ala Pro Ala Pro Pro Gln Val Leu Pro Gln Ala Pro Ala Pro Ala
625                 630                 635                 640
Pro Ala Pro Ala Met Val Ser Ala Leu Ala Gln Ala Pro Ala Pro Val
                645                 650                 655
Pro Val Leu Ala Pro Gly Pro Pro Gln Ala Val Ala Pro Pro Ala Pro
            660                 665                 670
Lys Pro Thr Gln Ala Gly Glu Gly Thr Leu Ser Glu Ala Leu Leu Gln
        675                 680                 685
Leu Gln Phe Asp Asp Glu Asp Leu Gly Ala Leu Leu Gly Asn Ser Thr
    690                 695                 700
Asp Pro Ala Val Phe Thr Asp Leu Ala Ser Val Asp Asn Ser Glu Phe
```

705 710 715 720
Gln Gln Leu Leu Asn Gln Gly Ile Pro Val Ala Pro His Thr Thr Glu
725 730 735
Pro Met Leu Met Glu Tyr Pro Glu Ala Ile Thr Arg Leu Val Thr Gly
740 745 750
Ala Gln Arg Pro Pro Asp Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly
755 760 765
Leu Pro Asn Gly Leu Leu Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala
770 775 780
Asp Met Asp Phe Ser Ala Leu Leu Ser Gln Ile Ser Ser
785 790 795

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3381 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3378
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

ATG GAG CGG GCC GGC CCC AGC TTC GGG CAG CAG CGA CAG CAG CAG CAG 48
Met Glu Arg Ala Gly Pro Ser Phe Gly Gln Gln Arg Gln Gln Gln Gln
1 5 10 15

CCC CAG CAG CAG AAG CAG CAG CAG AGG GAT CAG GAC TCG GTC GAA GCA 96
Pro Gln Gln Gln Lys Gln Gln Gln Arg Asp Gln Asp Ser Val Glu Ala
20 25 30

TGG CTG GAC GAT CAC TGG GAC TTT ACC TTC TCA TAC TTT GTT AGA AAA 144
Trp Leu Asp Asp His Trp Asp Phe Thr Phe Ser Tyr Phe Val Arg Lys
35 40 45

GCC ACC AGA GAA ATG GTC AAT GCA TGG TTT GCT GAG AGA GTT CAC ACC 192
Ala Thr Arg Glu Met Val Asn Ala Trp Phe Ala Glu Arg Val His Thr
50 55 60

ATC CCT GTG TGC AAG GAA GGT ATC AGA GGC CAC ACC GAA TCT TGC TCT 240
Ile Pro Val Cys Lys Glu Gly Ile Arg Gly His Thr Glu Ser Cys Ser
65 70 75 80

TGT CCC TTG CAG CAG AGT CCT CGT GCA GAT AAC AGT GTC CCT GGA ACA 288
Cys Pro Leu Gln Gln Ser Pro Arg Ala Asp Asn Ser Val Pro Gly Thr

85 90 95

CCA ACC AGG AAA ATC TCT GCC TCT GAA TTT GAC CGG CCT CTT AGA CCC 336
Pro Thr Arg Lys Ile Ser Ala Ser Glu Phe Asp Arg Pro Leu Arg Pro
100 105 110

ATT GTT GTC AAG GAT TCT GAG GGA ACT GTG AGC TTC CTC TCT GAC TCA 384
Ile Val Val Lys Asp Ser Glu Gly Thr Val Ser Phe Leu Ser Asp Ser
115 120 125

GAA AAG AAG GAA CAG ATG CCT CTA ACC CCT CCA AGG TTT GAT CAT GAT 432
Glu Lys Lys Glu Gln Met Pro Leu Thr Pro Pro Arg Phe Asp His Asp
130 135 140

GAA GGG GAC CAG TGC TCA AGA CTC TTG GAA TTA GTG AAG GAT ATT TCT 480
Glu Gly Asp Gln Cys Ser Arg Leu Leu Glu Leu Val Lys Asp Ile Ser
145 150 155 160

AGT CAT TTG GAT GTC ACA GCC TTA TGT CAC AAA ATT TTC TTG CAT ATC 528
Ser His Leu Asp Val Thr Ala Leu Cys His Lys Ile Phe Leu His Ile
165 170 175

CAT GGA CTG ATA TCT GCT GAC CGC TAT TCC CTG TTC CTT GTC TGT GAA 576
His Gly Leu Ile Ser Ala Asp Arg Tyr Ser Leu Phe Leu Val Cys Glu
180 185 190

GAC AGC TCC AAT GAC AAG TTT CTT ATC AGC CGC CTC TTT GAT GTT GCT 624
Asp Ser Ser Asn Asp Lys Phe Leu Ile Ser Arg Leu Phe Asp Val Ala
195 200 205

GAA GGT TCA ACA CTG GAA GAA GTT TCA AAT AAC TGT ATC CGC TTA GAA 672
Glu Gly Ser Thr Leu Glu Glu Val Ser Asn Asn Cys Ile Arg Leu Glu
210 215 220

TGG AAC AAA GGC ATT GTG GGA CAT GTG GCA GCG CTT GGT GAG CCC TTG 720
Trp Asn Lys Gly Ile Val Gly His Val Ala Ala Leu Gly Glu Pro Leu
225 230 235 240

AAC ATC AAA GAT GCA TAT GAG GAT CCT CGG TTC AAT GCA GAA GTT GAC 768
Asn Ile Lys Asp Ala Tyr Glu Asp Pro Arg Phe Asn Ala Glu Val Asp
245 250 255

CAA ATT ACA GGC TAC AAG ACA CAA AGC ATT CTT TGT ATG CCA ATT AAG 816
Gln Ile Thr Gly Tyr Lys Thr Gln Ser Ile Leu Cys Met Pro Ile Lys
260 265 270

AAT CAT AGG GAA GAG GTT GTT GGT GTA GCC CAG GCC ATC AAC AAG AAA 864
Asn His Arg Glu Glu Val Val Gly Val Ala Gln Ala Ile Asn Lys Lys
275 280 285

TCA GGA AAC GGT GGG ACA TTT ACT GAA AAA GAT GAA AAG GAC TTT GCT 912
Ser Gly Asn Gly Gly Thr Phe Thr Glu Lys Asp Glu Lys Asp Phe Ala
290 295 300

```
GCT TAT TTG GCA TTT TGT GGT ATT GTT CTT CAT AAT GCT CAG CTC TAT      960
Ala Tyr Leu Ala Phe Cys Gly Ile Val Leu His Asn Ala Gln Leu Tyr
305                 310                 315                 320

GAG ACT TCA CTG CTG GAG AAC AAG AGA AAT CAG GTG CTG CTT GAC CTT     1008
Glu Thr Ser Leu Leu Glu Asn Lys Arg Asn Gln Val Leu Leu Asp Leu
                325                 330                 335

GCT AGT TTA ATT TTT GAA GAA CAA CAA TCA TTA GAA GTA ATT TTG AAG     1056
Ala Ser Leu Ile Phe Glu Glu Gln Gln Ser Leu Glu Val Ile Leu Lys
            340                 345                 350

AAA ATA GCT GCC ACT ATT ATC TCT TTC ATG CAA GTG CAG AAA TGC ACC     1104
Lys Ile Ala Ala Thr Ile Ile Ser Phe Met Gln Val Gln Lys Cys Thr
        355                 360                 365

ATT TTC ATA GTG GAT GAA GAT TGC TCC GAT TCT TTT TCT AGT GTG TTT     1152
Ile Phe Ile Val Asp Glu Asp Cys Ser Asp Ser Phe Ser Ser Val Phe
    370                 375                 380

CAC ATG GAG TGT GAG GAA TTA GAA AAA TCA TCT GAT ACA TTA ACA AGG     1200
His Met Glu Cys Glu Glu Leu Glu Lys Ser Ser Asp Thr Leu Thr Arg
385                 390                 395                 400

GAA CAT GAT GCA AAC AAA ATC AAT TAC ATG TAT GCT CAG TAT GTC AAA     1248
Glu His Asp Ala Asn Lys Ile Asn Tyr Met Tyr Ala Gln Tyr Val Lys
                405                 410                 415

AAT ACT ATG GAA CCA CTT AAT ATC CCA GAT GTC AGT AAG GAT AAA AGA     1296
Asn Thr Met Glu Pro Leu Asn Ile Pro Asp Val Ser Lys Asp Lys Arg
            420                 425                 430

TTT CCC TGG ACA ACT GAA AAT ACA GGA AAT GTA AAC CAG CAG TGC ATT     1344
Phe Pro Trp Thr Thr Glu Asn Thr Gly Asn Val Asn Gln Gln Cys Ile
        435                 440                 445

AGA AGT TTG CTT TGT ACA CCT ATA AAA AAT GGA AAG AAG AAT AAA GTT     1392
Arg Ser Leu Leu Cys Thr Pro Ile Lys Asn Gly Lys Lys Asn Lys Val
    450                 455                 460

ATA GGG GTT TGC CAA CTT GTT AAT AAG ATG GAG GAG AAT ACT GGC AAG     1440
Ile Gly Val Cys Gln Leu Val Asn Lys Met Glu Glu Asn Thr Gly Lys
465                 470                 475                 480

GTT AAG CCT TTC AAC CGA AAT GAC GAA CAG TTT CTG GAA GCT TTT GTC     1488
Val Lys Pro Phe Asn Arg Asn Asp Glu Gln Phe Leu Glu Ala Phe Val
                485                 490                 495

ATC TTT TGT GGC TTG GGG ATC CAG AAC ACG CAG ATG TAT GAA GCA GTG     1536
Ile Phe Cys Gly Leu Gly Ile Gln Asn Thr Gln Met Tyr Glu Ala Val
            500                 505                 510

GAG AGA GCC ATG GCC AAG CAA ATG GTC ACA TTG GAG GTT CTG TCG TAT     1584
Glu Arg Ala Met Ala Lys Gln Met Val Thr Leu Glu Val Leu Ser Tyr
```

515 520 525

CAT GCT TCA GCA GCA GAG GAA GAA ACA AGA GAG CTA CAG TCG TTA GCG 1632
His Ala Ser Ala Ala Glu Glu Glu Thr Arg Glu Leu Gln Ser Leu Ala
530 535 540

GCT GCT GTG GTG CCA TCT GCC CAG ACC CTT AAA ATT ACT GAC TTT AGC 1680
Ala Ala Val Val Pro Ser Ala Gln Thr Leu Lys Ile Thr Asp Phe Ser
545 550 555 560

TTC AGT GAC TTT GAG CTG TCT GAT CTG GAA ACA GCA CTG TGC ACA ATT 1728
Phe Ser Asp Phe Glu Leu Ser Asp Leu Glu Thr Ala Leu Cys Thr Ile
565 570 575

CGG ATG TTT ACT GAC CTC AAC CTT GTG CAG AAC TTC CAG ATG AAA CAT 1776
Arg Met Phe Thr Asp Leu Asn Leu Val Gln Asn Phe Gln Met Lys His
580 585 590

GAG GTT CTT TGC AGA TGG ATT TTA AGT GTT AAG AAG AAT TAT CGG AAG 1824
Glu Val Leu Cys Arg Trp Ile Leu Ser Val Lys Lys Asn Tyr Arg Lys
595 600 605

AAT GTT GCC TAT CAT AAT TGG AGA CAT GCC TTT AAT ACA GCT CAG TGC 1872
Asn Val Ala Tyr His Asn Trp Arg His Ala Phe Asn Thr Ala Gln Cys
610 615 620

ATG TTT GCT GCT CTA AAA GCA GGC AAA ATT CAG AAC AAG CTG ACT GAC 1920
Met Phe Ala Ala Leu Lys Ala Gly Lys Ile Gln Asn Lys Leu Thr Asp
625 630 635 640

CTG GAG ATA CTT GCA TTG CTG ATT GCT GCA CTA AGC CAC GAT TTG GAT 1968
Leu Glu Ile Leu Ala Leu Leu Ile Ala Ala Leu Ser His Asp Leu Asp
645 650 655

CAC CGT GGT GTG AAT AAC TCT TAC ATA CAG CGA AGT GAA CAT CCA CTT 2016
His Arg Gly Val Asn Asn Ser Tyr Ile Gln Arg Ser Glu His Pro Leu
660 665 670

GCC CAG CTT TAC TGC CAT TCA ATC ATG GAA CAC CAT CAT TTT GAC CAG 2064
Ala Gln Leu Tyr Cys His Ser Ile Met Glu His His His Phe Asp Gln
675 680 685

TGC CTG ATG ATT CTT AAT AGT CCA GGC AAT CAG ATT CTC AGT GGC CTC 2112
Cys Leu Met Ile Leu Asn Ser Pro Gly Asn Gln Ile Leu Ser Gly Leu
690 695 700

TCC ATT GAA GAA TAT AAG ACC ACG TTG AAA ATA ATC AAG CAA GCT ATT 2160
Ser Ile Glu Glu Tyr Lys Thr Thr Leu Lys Ile Ile Lys Gln Ala Ile
705 710 715 720

TTA GCT ACA GAC CTA GCA CTG TAC ATT AAG AGG CGA GGA GAA TTT TTT 2208
Leu Ala Thr Asp Leu Ala Leu Tyr Ile Lys Arg Arg Gly Glu Phe Phe
725 730 735

GAA CTT ATA AGA AAA AAT CAA TTC AAT TTG GAA GAT CCT CAT CAA AAG 2256
Glu Leu Ile Arg Lys Asn Gln Phe Asn Leu Glu Asp Pro His Gln Lys
740 745 750

GAG TTG TTT TTG GCA ATG CTG ATG ACA GCT TGT GAT CTT TCT GCA ATT 2304
Glu Leu Phe Leu Ala Met Leu Met Thr Ala Cys Asp Leu Ser Ala Ile
755 760 765

ACA AAA CCC TGG CCT ATT CAA CAA CGG ATA GCA GAA CTT GTA GCA ACT 2352
Thr Lys Pro Trp Pro Ile Gln Gln Arg Ile Ala Glu Leu Val Ala Thr
770 775 780

GAA TTT TTT GAT CAA GGA GAC AGA GAG AGA AAA GAA CTC AAC ATA GAA 2400
Glu Phe Phe Asp Gln Gly Asp Arg Glu Arg Lys Glu Leu Asn Ile Glu
785 790 795 800

CCC ACT GAT CTA ATG AAC AGG GAG AAG AAA AAC AAA ATC CCA AGT ATG 2448
Pro Thr Asp Leu Met Asn Arg Glu Lys Lys Asn Lys Ile Pro Ser Met
805 810 815

CAA GTT GGG TTC ATA GAT GCC ATC TGC TTG CAA CTG TAT GAG GCC CTG 2496
Gln Val Gly Phe Ile Asp Ala Ile Cys Leu Gln Leu Tyr Glu Ala Leu
820 825 830

ACC CAC GTG TCA GAG GAC TGT TTC CCT TTG CTA GAT GGC TGC AGA AAG 2544
Thr His Val Ser Glu Asp Cys Phe Pro Leu Leu Asp Gly Cys Arg Lys
835 840 845

AAC AGG CAG AAA TGG CAG GCC CTT GCA GAA CAG CAG GAG AAG ATG CTG 2592
Asn Arg Gln Lys Trp Gln Ala Leu Ala Glu Gln Gln Glu Lys Met Leu
850 855 860

ATT AAT GGG GAA AGC GGC CAG GCC AAG CGG AAC TGG GTA CCG CGG GCC 2640
Ile Asn Gly Glu Ser Gly Gln Ala Lys Arg Asn Trp Val Pro Arg Ala
865 870 875 880

CGG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC 2688
Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
885 890 895

ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC 2736
Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
900 905 910

CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC 2784
His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
915 920 925

AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC 2832
Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro
930 935 940

TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC 2880
Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser

945 950 955 960

CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG 2928
Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
965 970 975

CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC 2976
Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
980 985 990

AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG 3024
Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val
995 1000 1005

AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC 3072
Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
1010 1015 1020

CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC 3120
Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
1025 1030 1035 1040

ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC 3168
Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
1045 1050 1055

CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG 3216
His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
1060 1065 1070

AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC 3264
Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
1075 1080 1085

CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT 3312
Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
1090 1095 1100

CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC 3360
His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
1105 1110 1115 1120

ATG GAC GAG CTG TAC AAG TAA 3381
Met Asp Glu Leu Tyr Lys
1125

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1126 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

```
Met Glu Arg Ala Gly Pro Ser Phe Gly Gln Gln Arg Gln Gln Gln Gln
1               5                   10                  15
Pro Gln Gln Gln Lys Gln Gln Gln Arg Asp Gln Asp Ser Val Glu Ala
            20                  25                  30
Trp Leu Asp Asp His Trp Asp Phe Thr Phe Ser Tyr Phe Val Arg Lys
        35                  40                  45
Ala Thr Arg Glu Met Val Asn Ala Trp Phe Ala Glu Arg Val His Thr
    50                  55                  60
Ile Pro Val Cys Lys Glu Gly Ile Arg Gly His Thr Glu Ser Cys Ser
65                  70                  75                  80
Cys Pro Leu Gln Gln Ser Pro Arg Ala Asp Asn Ser Val Pro Gly Thr
                85                  90                  95
Pro Thr Arg Lys Ile Ser Ala Ser Glu Phe Asp Arg Pro Leu Arg Pro
            100                 105                 110
Ile Val Val Lys Asp Ser Glu Gly Thr Val Ser Phe Leu Ser Asp Ser
        115                 120                 125
Glu Lys Lys Glu Gln Met Pro Leu Thr Pro Pro Arg Phe Asp His Asp
    130                 135                 140
Glu Gly Asp Gln Cys Ser Arg Leu Leu Glu Leu Val Lys Asp Ile Ser
145                 150                 155                 160
Ser His Leu Asp Val Thr Ala Leu Cys His Lys Ile Phe Leu His Ile
                165                 170                 175
His Gly Leu Ile Ser Ala Asp Arg Tyr Ser Leu Phe Leu Val Cys Glu
            180                 185                 190
Asp Ser Ser Asn Asp Lys Phe Leu Ile Ser Arg Leu Phe Asp Val Ala
        195                 200                 205
Glu Gly Ser Thr Leu Glu Glu Val Ser Asn Asn Cys Ile Arg Leu Glu
    210                 215                 220
Trp Asn Lys Gly Ile Val Gly His Val Ala Ala Leu Gly Glu Pro Leu
225                 230                 235                 240
Asn Ile Lys Asp Ala Tyr Glu Asp Pro Arg Phe Asn Ala Glu Val Asp
                245                 250                 255
Gln Ile Thr Gly Tyr Lys Thr Gln Ser Ile Leu Cys Met Pro Ile Lys
            260                 265                 270
Asn His Arg Glu Glu Val Val Gly Val Ala Gln Ala Ile Asn Lys Lys
        275                 280                 285
Ser Gly Asn Gly Gly Thr Phe Thr Glu Lys Asp Glu Lys Asp Phe Ala
    290                 295                 300
Ala Tyr Leu Ala Phe Cys Gly Ile Val Leu His Asn Ala Gln Leu Tyr
305                 310                 315                 320
Glu Thr Ser Leu Leu Glu Asn Lys Arg Asn Gln Val Leu Leu Asp Leu
                325                 330                 335
Ala Ser Leu Ile Phe Glu Glu Gln Gln Ser Leu Glu Val Ile Leu Lys
            340                 345                 350
Lys Ile Ala Ala Thr Ile Ile Ser Phe Met Gln Val Gln Lys Cys Thr
        355                 360                 365
Ile Phe Ile Val Asp Glu Asp Cys Ser Asp Ser Phe Ser Ser Val Phe
    370                 375                 380
```

His Met Glu Cys Glu Glu Leu Glu Lys Ser Ser Asp Thr Leu Thr Arg
385 390 395 400
Glu His Asp Ala Asn Lys Ile Asn Tyr Met Tyr Ala Gln Tyr Val Lys
405 410 415
Asn Thr Met Glu Pro Leu Asn Ile Pro Asp Val Ser Lys Asp Lys Arg
420 425 430
Phe Pro Trp Thr Thr Glu Asn Thr Gly Asn Val Asn Gln Gln Cys Ile
435 440 445
Arg Ser Leu Leu Cys Thr Pro Ile Lys Asn Gly Lys Lys Asn Lys Val
450 455 460
Ile Gly Val Cys Gln Leu Val Asn Lys Met Glu Glu Asn Thr Gly Lys
465 470 475 480
Val Lys Pro Phe Asn Arg Asn Asp Glu Gln Phe Leu Glu Ala Phe Val
485 490 495
Ile Phe Cys Gly Leu Gly Ile Gln Asn Thr Gln Met Tyr Glu Ala Val
500 505 510
Glu Arg Ala Met Ala Lys Gln Met Val Thr Leu Glu Val Leu Ser Tyr
515 520 525
His Ala Ser Ala Ala Glu Glu Glu Thr Arg Glu Leu Gln Ser Leu Ala
530 535 540
Ala Ala Val Val Pro Ser Ala Gln Thr Leu Lys Ile Thr Asp Phe Ser
545 550 555 560
Phe Ser Asp Phe Glu Leu Ser Asp Leu Glu Thr Ala Leu Cys Thr Ile
565 570 575
Arg Met Phe Thr Asp Leu Asn Leu Val Gln Asn Phe Gln Met Lys His
580 585 590
Glu Val Leu Cys Arg Trp Ile Leu Ser Val Lys Lys Asn Tyr Arg Lys
595 600 605
Asn Val Ala Tyr His Asn Trp Arg His Ala Phe Asn Thr Ala Gln Cys
610 615 620
Met Phe Ala Ala Leu Lys Ala Gly Lys Ile Gln Asn Lys Leu Thr Asp
625 630 635 640
Leu Glu Ile Leu Ala Leu Leu Ile Ala Ala Leu Ser His Asp Leu Asp
645 650 655
His Arg Gly Val Asn Asn Ser Tyr Ile Gln Arg Ser Glu His Pro Leu
660 665 670
Ala Gln Leu Tyr Cys His Ser Ile Met Glu His His His Phe Asp Gln
675 680 685
Cys Leu Met Ile Leu Asn Ser Pro Gly Asn Gln Ile Leu Ser Gly Leu
690 695 700
Ser Ile Glu Glu Tyr Lys Thr Thr Leu Lys Ile Ile Lys Gln Ala Ile
705 710 715 720
Leu Ala Thr Asp Leu Ala Leu Tyr Ile Lys Arg Arg Gly Glu Phe Phe
725 730 735
Glu Leu Ile Arg Lys Asn Gln Phe Asn Leu Glu Asp Pro His Gln Lys
740 745 750
Glu Leu Phe Leu Ala Met Leu Met Thr Ala Cys Asp Leu Ser Ala Ile
755 760 765
Thr Lys Pro Trp Pro Ile Gln Gln Arg Ile Ala Glu Leu Val Ala Thr
770 775 780
Glu Phe Phe Asp Gln Gly Asp Arg Glu Arg Lys Glu Leu Asn Ile Glu
785 790 795 800
Pro Thr Asp Leu Met Asn Arg Glu Lys Lys Asn Lys Ile Pro Ser Met
805 810 815

Gln Val Gly Phe Ile Asp Ala Ile Cys Leu Gln Leu Tyr Glu Ala Leu
820 825 830

Thr His Val Ser Glu Asp Cys Phe Pro Leu Leu Asp Gly Cys Arg Lys
835 840 845

Asn Arg Gln Lys Trp Gln Ala Leu Ala Glu Gln Gln Glu Lys Met Leu
850 855 860

Ile Asn Gly Glu Ser Gly Gln Ala Lys Arg Asn Trp Val Pro Arg Ala
865 870 875 880

Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe
885 890 895

Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly
900 905 910

His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly
915 920 925

Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro
930 935 940

Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser
945 950 955 960

Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met
965 970 975

Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly
980 985 990

Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val
995 1000 1005

Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile
1010 1015 1020

Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile
025 1030 1035 1040

Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg
1045 1050 1055

His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln
1060 1065 1070

Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr
1075 1080 1085

Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp
1090 1095 1100

His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly
105 1110 1115 1120

Met Asp Glu Leu Tyr Lys
1125

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2760 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2757

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

ATG GCT GAC CCG GCT GCG GGG CCG CCG CCG AGC GAG GGC GAG GAG AGC 48
Met Ala Asp Pro Ala Ala Gly Pro Pro Pro Ser Glu Gly Glu Glu Ser
1 5 10 15

ACC GTG CGC TTC GCC CGC AAA GGC GCC CTC CGG CAG AAG AAC GTG CAT 96
Thr Val Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
20 25 30

GAG GTC AAG AAC CAC AAA TTC ACC GCC CGC TTC TTC AAG CAG CCC ACC 144
Glu Val Lys Asn His Lys Phe Thr Ala Arg Phe Phe Lys Gln Pro Thr
35 40 45

TTC TGC AGC CAC TGC ACC GAC TTC ATC TGG GGC TTC GGG AAG CAG GGA 192
Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly
50 55 60

TTC CAG TGC CAA GTT TGC TGC TTT GTG GTG CAC AAG CGG TGC CAT GAA 240
Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
65 70 75 80

TTT GTC ACA TTC TCC TGC CCT GGC GCT GAC AAG GGT CCA GCC TCC GAT 288
Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Ala Ser Asp
85 90 95

GAC CCC CGC AGC AAA CAC AAG TTT AAG ATC CAC ACG TAC TCC AGC CCC 336
Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Ser Ser Pro
100 105 110

ACG TTT TGT GAC CAC TGT GGG TCA CTG CTG TAT GGA CTC ATC CAC CAG 384
Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
115 120 125

GGG ATG AAA TGT GAC ACC TGC ATG ATG AAT GTG CAC AAG CGC TGC GTG 432
Gly Met Lys Cys Asp Thr Cys Met Met Asn Val His Lys Arg Cys Val
130 135 140

ATG AAT GTT CCC AGC CTG TGT GGC ACG GAC CAC ACG GAG CGC CGC GGC 480
Met Asn Val Pro Ser Leu Cys Gly Thr Asp His Thr Glu Arg Arg Gly
145 150 155 160

CGC ATC TAC ATC CAG GCC CAC ATC GAC AGG GAC GTC CTC ATT GTC CTC 528
Arg Ile Tyr Ile Gln Ala His Ile Asp Arg Asp Val Leu Ile Val Leu
165 170 175

GTA AGA GAT GCT AAA AAC CTT GTA CCT ATG GAC CCC AAT GGC CTG TCA 576
Val Arg Asp Ala Lys Asn Leu Val Pro Met Asp Pro Asn Gly Leu Ser
180 185 190

GAT CCC TAC GTA AAA CTG AAA CTG ATT CCC GAT CCC AAA AGT GAG AGC 624
Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Ser Glu Ser

195 200 205

AAA CAG AAG ACC AAA ACC ATC AAA TGC TCC CTC AAC CCT GAG TGG AAT 672
Lys Gln Lys Thr Lys Thr Ile Lys Cys Ser Leu Asn Pro Glu Trp Asn
210 215 220

GAG ACA TTT AGA TTT CAG CTG AAA GAA TCG GAC AAA GAC AGA AGA CTG 720
Glu Thr Phe Arg Phe Gln Leu Lys Glu Ser Asp Lys Asp Arg Arg Leu
225 230 235 240

TCA GTA GAG ATT TGG GAT TGG GAT TTG ACC AGC AGG AAT GAC TTC ATG 768
Ser Val Glu Ile Trp Asp Trp Asp Leu Thr Ser Arg Asn Asp Phe Met
245 250 255

GGA TCT TTG TCC TTT GGG ATT TCT GAA CTT CAG AAG GCC AGT GTT GAT 816
Gly Ser Leu Ser Phe Gly Ile Ser Glu Leu Gln Lys Ala Ser Val Asp
260 265 270

GGC TGG TTT AAG TTA CTG AGC CAG GAG GAA GGC GAG TAC TTC AAT GTG 864
Gly Trp Phe Lys Leu Leu Ser Gln Glu Glu Gly Glu Tyr Phe Asn Val
275 280 285

CCT GTG CCA CCA GAA GGA AGT GAG GCC AAT GAA GAA CTG CGG CAG AAA 912
Pro Val Pro Pro Glu Gly Ser Glu Ala Asn Glu Glu Leu Arg Gln Lys
290 295 300

TTT GAG AGG GCC AAG ATC AGT CAG GGA ACC AAG GTC CCG GAA GAA AAG 960
Phe Glu Arg Ala Lys Ile Ser Gln Gly Thr Lys Val Pro Glu Glu Lys
305 310 315 320

ACG ACC AAC ACT GTC TCC AAA TTT GAC AAC AAT GGC AAC AGA GAC CGG 1008
Thr Thr Asn Thr Val Ser Lys Phe Asp Asn Asn Gly Asn Arg Asp Arg
325 330 335

ATG AAA CTG ACC GAT TTT AAC TTC CTA ATG GTG CTG GGG AAA GGC AGC 1056
Met Lys Leu Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser
340 345 350

TTT GGC AAG GTC ATG CTT TCA GAA CGA AAA GGC ACA GAT GAG CTC TAT 1104
Phe Gly Lys Val Met Leu Ser Glu Arg Lys Gly Thr Asp Glu Leu Tyr
355 360 365

GCT GTG AAG ATC CTG AAG AAG GAC GTT GTG ATC CAA GAT GAT GAC GTG 1152
Ala Val Lys Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val
370 375 380

GAG TGC ACT ATG GTG GAG AAG CGG GTG TTG GCC CTG CCT GGG AAG CCG 1200
Glu Cys Thr Met Val Glu Lys Arg Val Leu Ala Leu Pro Gly Lys Pro
385 390 395 400

CCC TTC CTG ACC CAG CTC CAC TCC TGC TTC CAG ACC ATG GAC CGC CTG 1248
Pro Phe Leu Thr Gln Leu His Ser Cys Phe Gln Thr Met Asp Arg Leu
405 410 415

TAC TTT GTG ATG GAG TAC GTG AAT GGG GGC GAC CTC ATG TAT CAC ATC 1296
Tyr Phe Val Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile
420 425 430

CAG CAA GTC GGC CGG TTC AAG GAG CCC CAT GCT GTA TTT TAC GCT GCA 1344
Gln Gln Val Gly Arg Phe Lys Glu Pro His Ala Val Phe Tyr Ala Ala
435 440 445

GAA ATT GCC ATC GGT CTG TTC TTC TTA CAG AGT AAG GGC ATC ATT TAC 1392
Glu Ile Ala Ile Gly Leu Phe Phe Leu Gln Ser Lys Gly Ile Ile Tyr
450 455 460

CGT GAC CTA AAA CTT GAC AAC GTG ATG CTC GAT TCT GAG GGA CAC ATC 1440
Arg Asp Leu Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile
465 470 475 480

AAG ATT GCC GAT TTT GGC ATG TGT AAG GAA AAC ATC TGG GAT GGG GTG 1488
Lys Ile Ala Asp Phe Gly Met Cys Lys Glu Asn Ile Trp Asp Gly Val
485 490 495

ACA ACC AAG ACA TTC TGT GGC ACT CCA GAC TAC ATC GCC CCC GAG ATA 1536
Thr Thr Lys Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile
500 505 510

ATT GCT TAT CAG CCC TAT GGG AAG TCC GTG GAT TGG TGG GCA TTT GGA 1584
Ile Ala Tyr Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Phe Gly
515 520 525

GTC CTG CTG TAT GAA ATG TTG GCT GGG CAG GCA CCC TTT GAA GGG GAG 1632
Val Leu Leu Tyr Glu Met Leu Ala Gly Gln Ala Pro Phe Glu Gly Glu
530 535 540

GAT GAA GAT GAA CTC TTC CAA TCC ATC ATG GAA CAC AAC GTA GCC TAT 1680
Asp Glu Asp Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ala Tyr
545 550 555 560

CCC AAG TCT ATG TCC AAG GAA GCT GTG GCC ATC TGC AAA GGG CTG ATG 1728
Pro Lys Ser Met Ser Lys Glu Ala Val Ala Ile Cys Lys Gly Leu Met
565 570 575

ACC AAA CAC CCA GGC AAA CGT CTG GGT TGT GGA CCT GAA GGC GAA CGT 1776
Thr Lys His Pro Gly Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg
580 585 590

GAT ATC AAA GAG CAT GCA TTT TTC CGG TAT ATT GAT TGG GAG AAA CTT 1824
Asp Ile Lys Glu His Ala Phe Phe Arg Tyr Ile Asp Trp Glu Lys Leu
595 600 605

GAA CGC AAA GAG ATC CAG CCC CCT TAT AAG CCA AAA GCT TGT GGG CGA 1872
Glu Arg Lys Glu Ile Gln Pro Pro Tyr Lys Pro Lys Ala Cys Gly Arg
610 615 620

AAT GCT GAA AAC TTC GAC CGA TTT TTC ACC CGC CAT CCA CCA GTC CTA 1920
Asn Ala Glu Asn Phe Asp Arg Phe Phe Thr Arg His Pro Pro Val Leu

625 630 635 640

ACA CCT CCC GAC CAG GAA GTC ATC AGG AAT ATT GAC CAA TCA GAA TTC 1968
Thr Pro Pro Asp Gln Glu Val Ile Arg Asn Ile Asp Gln Ser Glu Phe
645 650 655

GAA GGA TTT TCC TTT GTT AAC TCT GAA TTT TTA AAA CCC GAA GTC AAG 2016
Glu Gly Phe Ser Phe Val Asn Ser Glu Phe Leu Lys Pro Glu Val Lys
660 665 670

AGC TCG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG 2064
Ser Ser Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu
675 680 685

TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC 2112
Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn
690 695 700

GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC 2160
Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr
705 710 715 720

GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG 2208
Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val
725 730 735

CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC 2256
Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe
740 745 750

AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC 2304
Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala
755 760 765

ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC 2352
Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp
770 775 780

GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG 2400
Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu
785 790 795 800

GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC 2448
Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn
805 810 815

ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT 2496
Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr
820 825 830

ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC 2544
Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile
835 840 845

```
CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG     2592
Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln
    850                 855                 860

CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC     2640
Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His
865                 870                 875                 880

TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC     2688
Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg
                885                 890                 895

GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC     2736
Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu
            900                 905                 910

GGC ATG GAC GAG CTG TAC AAG TAA                                      2760
Gly Met Asp Glu Leu Tyr Lys
        915
```

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 919 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

```
Met Ala Asp Pro Ala Ala Gly Pro Pro Pro Ser Glu Gly Glu Glu Ser
 1              5                   10                  15
Thr Val Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
            20                  25                  30
Glu Val Lys Asn His Lys Phe Thr Ala Arg Phe Phe Lys Gln Pro Thr
        35                  40                  45
Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly
    50                  55                  60
Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
65                  70                  75                  80
Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Ala Ser Asp
                85                  90                  95
Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Ser Ser Pro
            100                 105                 110
Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
        115                 120                 125
Gly Met Lys Cys Asp Thr Cys Met Met Asn Val His Lys Arg Cys Val
    130                 135                 140
Met Asn Val Pro Ser Leu Cys Gly Thr Asp His Thr Glu Arg Arg Gly
145                 150                 155                 160
```

```
Arg Ile Tyr Ile Gln Ala His Ile Asp Arg Asp Val Leu Ile Val Leu
                165                 170                 175
Val Arg Asp Ala Lys Asn Leu Val Pro Met Asp Pro Asn Gly Leu Ser
            180                 185                 190
Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Ser Glu Ser
        195                 200                 205
Lys Gln Lys Thr Lys Thr Ile Lys Cys Ser Leu Asn Pro Glu Trp Asn
    210                 215                 220
Glu Thr Phe Arg Phe Gln Leu Lys Glu Ser Asp Lys Asp Arg Arg Leu
225                 230                 235                 240
Ser Val Glu Ile Trp Asp Trp Asp Leu Thr Ser Arg Asn Asp Phe Met
                245                 250                 255
Gly Ser Leu Ser Phe Gly Ile Ser Glu Leu Gln Lys Ala Ser Val Asp
            260                 265                 270
Gly Trp Phe Lys Leu Leu Ser Gln Glu Glu Gly Glu Tyr Phe Asn Val
        275                 280                 285
Pro Val Pro Pro Glu Gly Ser Glu Ala Asn Glu Glu Leu Arg Gln Lys
    290                 295                 300
Phe Glu Arg Ala Lys Ile Ser Gln Gly Thr Lys Val Pro Glu Glu Lys
305                 310                 315                 320
Thr Thr Asn Thr Val Ser Lys Phe Asp Asn Asn Gly Asn Arg Asp Arg
                325                 330                 335
Met Lys Leu Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser
            340                 345                 350
Phe Gly Lys Val Met Leu Ser Glu Arg Lys Gly Thr Asp Glu Leu Tyr
        355                 360                 365
Ala Val Lys Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val
    370                 375                 380
Glu Cys Thr Met Val Glu Lys Arg Val Leu Ala Leu Pro Gly Lys Pro
385                 390                 395                 400
Pro Phe Leu Thr Gln Leu His Ser Cys Phe Gln Thr Met Asp Arg Leu
                405                 410                 415
Tyr Phe Val Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile
            420                 425                 430
Gln Gln Val Gly Arg Phe Lys Glu Pro His Ala Val Phe Tyr Ala Ala
        435                 440                 445
Glu Ile Ala Ile Gly Leu Phe Phe Leu Gln Ser Lys Gly Ile Ile Tyr
    450                 455                 460
Arg Asp Leu Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile
465                 470                 475                 480
Lys Ile Ala Asp Phe Gly Met Cys Lys Glu Asn Ile Trp Asp Gly Val
                485                 490                 495
Thr Thr Lys Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile
            500                 505                 510
Ile Ala Tyr Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Phe Gly
        515                 520                 525
Val Leu Leu Tyr Glu Met Leu Ala Gly Gln Ala Pro Phe Glu Gly Glu
    530                 535                 540
Asp Glu Asp Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ala Tyr
545                 550                 555                 560
Pro Lys Ser Met Ser Lys Glu Ala Val Ala Ile Cys Lys Gly Leu Met
                565                 570                 575
Thr Lys His Pro Gly Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg
            580                 585                 590
```

```
Asp Ile Lys Glu His Ala Phe Phe Arg Tyr Ile Asp Trp Glu Lys Leu
        595                 600                 605
Glu Arg Lys Glu Ile Gln Pro Pro Tyr Lys Pro Lys Ala Cys Gly Arg
    610                 615                 620
Asn Ala Glu Asn Phe Asp Arg Phe Phe Thr Arg His Pro Pro Val Leu
625                 630                 635                 640
Thr Pro Pro Asp Gln Glu Val Ile Arg Asn Ile Asp Gln Ser Glu Phe
                645                 650                 655
Glu Gly Phe Ser Phe Val Asn Ser Glu Phe Leu Lys Pro Glu Val Lys
            660                 665                 670
Ser Ser Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu
        675                 680                 685
Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn
    690                 695                 700
Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr
705                 710                 715                 720
Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val
                725                 730                 735
Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe
            740                 745                 750
Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala
        755                 760                 765
Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp
    770                 775                 780
Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu
785                 790                 795                 800
Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn
                805                 810                 815
Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr
            820                 825                 830
Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile
        835                 840                 845
Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln
    850                 855                 860
Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His
865                 870                 875                 880
Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg
                885                 890                 895
Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu
            900                 905                 910
Gly Met Asp Glu Leu Tyr Lys
        915
```

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 3009 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3006
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

```
ATG GCT CAG CAG ACA AGC CCG GAC ACT TTA ACA GTA CCT GAA GTG GAT      48
Met Ala Gln Gln Thr Ser Pro Asp Thr Leu Thr Val Pro Glu Val Asp
 1               5                  10                  15

AAT CCG CAT TGT CCA AAC CCG TGG CTG AAC GAA GAC CTT GTG AAA TCC      96
Asn Pro His Cys Pro Asn Pro Trp Leu Asn Glu Asp Leu Val Lys Ser
            20                  25                  30

TTG CGA GAA AAC CTG TTG CAG CAT GAG AAG TCC AAG ACA GCG AGG AAA     144
Leu Arg Glu Asn Leu Leu Gln His Glu Lys Ser Lys Thr Ala Arg Lys
        35                  40                  45

TCG GTT TCT CCC AAG CTC TCT CCA GTG ATC TCT CCG AGA AAT TCC CCC     192
Ser Val Ser Pro Lys Leu Ser Pro Val Ile Ser Pro Arg Asn Ser Pro
    50                  55                  60

AGG CTT CTG CGC AGA ATG CTT CTC AGC AGC AAC ATC CCC AAA CAG CGG     240
Arg Leu Leu Arg Arg Met Leu Leu Ser Ser Asn Ile Pro Lys Gln Arg
65                  70                  75                  80

CGT TTC ACG GTG GCA CAT ACA TGT TTT GAT GTG GAC AAT GGC ACA TCT     288
Arg Phe Thr Val Ala His Thr Cys Phe Asp Val Asp Asn Gly Thr Ser
                85                  90                  95

GCG GGA CGG AGT CCC TTG GAT CCC ATG ACC AGC CCA GGA TCC GGG CTA     336
Ala Gly Arg Ser Pro Leu Asp Pro Met Thr Ser Pro Gly Ser Gly Leu
            100                 105                 110

ATT CTC CAA GCA AAT TTT GTC CAC AGT CAA CGA CGG GAG TCC TTC CTG     384
Ile Leu Gln Ala Asn Phe Val His Ser Gln Arg Arg Glu Ser Phe Leu
        115                 120                 125

TAT CGA TCC GAC AGC GAT TAT GAC CTC TCT CCA AAG TCT ATG TCC CGG     432
Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ser Met Ser Arg
    130                 135                 140

AAC TCC TCC ATT GCC AGT GAT ATA CAC GGA GAT GAC TTG ATT GTG ACT     480
Asn Ser Ser Ile Ala Ser Asp Ile His Gly Asp Asp Leu Ile Val Thr
145                 150                 155                 160

CCA TTT GCT CAG GTC TTG GCC AGT CTG CGA ACT GTA CGA AAC AAC TTT     528
Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Thr Val Arg Asn Asn Phe
                165                 170                 175

GCT GCA TTA ACT AAT TTG CAA GAT CGA GCA CCT AGC AAA AGA TCA CCC     576
Ala Ala Leu Thr Asn Leu Gln Asp Arg Ala Pro Ser Lys Arg Ser Pro
            180                 185                 190
```

```
ATG TGC AAC CAA CCA TCC ATC AAC AAA GCC ACC ATA ACA GAG GAG GCC     624
Met Cys Asn Gln Pro Ser Ile Asn Lys Ala Thr Ile Thr Glu Glu Ala
        195                 200                 205

TAC CAG AAA CTG GCC AGC GAG ACC CTG GAG GAG CTG GAC TGG TGT CTG     672
Tyr Gln Lys Leu Ala Ser Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu
    210                 215                 220

GAC CAG CTA GAG ACC CTA CAG ACC AGG CAC TCC GTC AGT GAG ATG GCC     720
Asp Gln Leu Glu Thr Leu Gln Thr Arg His Ser Val Ser Glu Met Ala
225                 230                 235                 240

TCC AAC AAG TTT AAA AGG ATG CTT AAT CGG GAG CTC ACC CAT CTC TCT     768
Ser Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser
                245                 250                 255

GAA ATG AGT CGG TCT GGA AAT CAA GTG TCA GAG TTT ATA TCA AAC ACA     816
Glu Met Ser Arg Ser Gly Asn Gln Val Ser Glu Phe Ile Ser Asn Thr
            260                 265                 270

TTC TTA GAT AAG CAA CAT GAA GTG GAA ATT CCT TCT CCA ACT CAG AAG     864
Phe Leu Asp Lys Gln His Glu Val Glu Ile Pro Ser Pro Thr Gln Lys
        275                 280                 285

GAA AAG GAG AAA AAG AAA AGA CCA ATG TCT CAG ATC AGT GGA GTC AAG     912
Glu Lys Glu Lys Lys Lys Arg Pro Met Ser Gln Ile Ser Gly Val Lys
    290                 295                 300

AAA TTG ATG CAC AGC TCT AGT CTG ACT AAT TCA AGT ATC CCA AGG TTT     960
Lys Leu Met His Ser Ser Ser Leu Thr Asn Ser Ser Ile Pro Arg Phe
305                 310                 315                 320

GGA GTT AAA ACT GAA CAA GAA GAT GTC CTT GCC AAG GAA CTA GAA GAT    1008
Gly Val Lys Thr Glu Gln Glu Asp Val Leu Ala Lys Glu Leu Glu Asp
                325                 330                 335

GTG AAC AAA TGG GGT CTT CAT GTT TTC AGA ATA GCA GAG TTG TCT GGT    1056
Val Asn Lys Trp Gly Leu His Val Phe Arg Ile Ala Glu Leu Ser Gly
            340                 345                 350

AAC CGG CCC TTG ACT GTT ATC ATG CAC ACC ATT TTT CAG GAA CGG GAT    1104
Asn Arg Pro Leu Thr Val Ile Met His Thr Ile Phe Gln Glu Arg Asp
        355                 360                 365

TTA TTA AAA ACA TTT AAA ATT CCA GTA GAT ACT TTA ATT ACA TAT CTT    1152
Leu Leu Lys Thr Phe Lys Ile Pro Val Asp Thr Leu Ile Thr Tyr Leu
    370                 375                 380

ATG ACT CTC GAA GAC CAT TAC CAT GCT GAT GTG GCC TAT CAC AAC AAT    1200
Met Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr His Asn Asn
385                 390                 395                 400

ATC CAT GCT GCA GAT GTT GTC CAG TCT ACT CAT GTG CTA TTA TCT ACA    1248
Ile His Ala Ala Asp Val Val Gln Ser Thr His Val Leu Leu Ser Thr
```

405 410 415

CCT GCT TTG GAG GCT GTG TTT ACA GAT TTG GAG ATT CTT GCA GCA ATT 1296
Pro Ala Leu Glu Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile
420 425 430

TTT GCC AGT GCA ATA CAT GAT GTA GAT CAT CCT GGT GTG TCC AAT CAA 1344
Phe Ala Ser Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln
435 440 445

TTT CTG ATC AAT ACA AAC TCT GAA CTT GCC TTG ATG TAC AAT GAT TCC 1392
Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Ser
450 455 460

TCA GTC TTA GAG AAC CAT CAT TTG GCT GTG GGC TTT AAA TTG CTT CAG 1440
Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln
465 470 475 480

GAA GAA AAC TGT GAC ATT TTC CAG AAT TTG ACC AAA AAA CAA AGA CAA 1488
Glu Glu Asn Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln
485 490 495

TCT TTA AGG AAA ATG GTC ATT GAC ATC GTA CTT GCA ACA GAT ATG TCA 1536
Ser Leu Arg Lys Met Val Ile Asp Ile Val Leu Ala Thr Asp Met Ser
500 505 510

AAA CAC ATG AAT CTA CTG GCT GAT TTG AAG ACT ATG GTT GAA ACT AAG 1584
Lys His Met Asn Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys
515 520 525

AAA GTG ACA AGC TCT GGA GTT CTT CTT CTT GAT AAT TAT TCC GAT AGG 1632
Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg
530 535 540

ATT CAG GTT CTT CAG AAT ATG GTG CAC TGT GCA GAT CTG AGC AAC CCA 1680
Ile Gln Val Leu Gln Asn Met Val His Cys Ala Asp Leu Ser Asn Pro
545 550 555 560

ACA AAG CCT CTC CAG CTG TAC CGC CAG TGG ACG GAC CGG ATA ATG GAG 1728
Thr Lys Pro Leu Gln Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu
565 570 575

GAG TTC TTC CGC CAA GGA GAC CGA GAG AGG GAA CGT GGC ATG GAG ATA 1776
Glu Phe Phe Arg Gln Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile
580 585 590

AGC CCC ATG TGT GAC AAG CAC AAT GCT TCC GTG GAA AAA TCA CAG GTG 1824
Ser Pro Met Cys Asp Lys His Asn Ala Ser Val Glu Lys Ser Gln Val
595 600 605

GGC TTC ATA GAC TAT ATT GTT CAT CCC CTC TGG GAG ACA TGG GCA GAC 1872
Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp
610 615 620

CTC GTC CAC CCT GAC GCC CAG GAT ATT TTG GAC ACT TTG GAG GAC AAT 1920
Leu Val His Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn
625 630 635 640

CGT GAA TGG TAC CAG AGC ACA ATC CCT CAG AGC CCC TCT CCT GCA CCT 1968
Arg Glu Trp Tyr Gln Ser Thr Ile Pro Gln Ser Pro Ser Pro Ala Pro
645 650 655

GAT GAC CCA GAG GAG GGC CGG CAG GGT CAA ACT GAG AAA TTC CAG TTT 2016
Asp Asp Pro Glu Glu Gly Arg Gln Gly Gln Thr Glu Lys Phe Gln Phe
660 665 670

GAA CTA ACT TTA GAG GAA GAT GGT GAG TCA GAC ACG GAA AAG GAC AGT 2064
Glu Leu Thr Leu Glu Glu Asp Gly Glu Ser Asp Thr Glu Lys Asp Ser
675 680 685

GGC AGT CAA GTG GAA GAA GAC ACT AGC TGC AGT GAC TCC AAG ACT CTT 2112
Gly Ser Gln Val Glu Glu Asp Thr Ser Cys Ser Asp Ser Lys Thr Leu
690 695 700

TGT ACT CAA GAC TCA GAG TCT ACT GAA ATT CCC CTT GAT GAA CAG GTT 2160
Cys Thr Gln Asp Ser Glu Ser Thr Glu Ile Pro Leu Asp Glu Gln Val
705 710 715 720

GAA GAG GAG GCA GTA GGG GAA GAA GAG GAA AGC CAG CCT GAA GCC TGT 2208
Glu Glu Glu Ala Val Gly Glu Glu Glu Glu Ser Gln Pro Glu Ala Cys
725 730 735

GTC ATA GAT GAT CGT TCT CCT GAC ACG ACG GGA ATT CTG CAG TCG ACG 2256
Val Ile Asp Asp Arg Ser Pro Asp Thr Thr Gly Ile Leu Gln Ser Thr
740 745 750

GTA CCG CGG GCC CGG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC 2304
Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly
755 760 765

GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC 2352
Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly
770 775 780

GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT 2400
Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp
785 790 795 800

GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG 2448
Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys
805 810 815

CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG 2496
Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val
820 825 830

CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC 2544
Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe

835 840 845

AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC 2592
Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe
850 855 860

AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC 2640
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
865 870 875 880

GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG 2688
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
885 890 895

GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC 2736
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
900 905 910

AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC 2784
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
915 920 925

TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC 2832
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
930 935 940

CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC 2880
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
945 950 955 960

GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC 2928
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
965 970 975

GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG 2976
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
980 985 990

ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 3009
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
995 1000

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1002 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

```
Met Ala Gln Gln Thr Ser Pro Asp Thr Leu Thr Val Pro Glu Val Asp
 1               5                  10                  15
Asn Pro His Cys Pro Asn Pro Trp Leu Asn Glu Asp Leu Val Lys Ser
            20                  25                  30
Leu Arg Glu Asn Leu Leu Gln His Glu Lys Ser Lys Thr Ala Arg Lys
        35                  40                  45
Ser Val Ser Pro Lys Leu Ser Pro Val Ile Ser Pro Arg Asn Ser Pro
    50                  55                  60
Arg Leu Leu Arg Arg Met Leu Leu Ser Ser Asn Ile Pro Lys Gln Arg
65                  70                  75                  80
Arg Phe Thr Val Ala His Thr Cys Phe Asp Val Asp Asn Gly Thr Ser
                85                  90                  95
Ala Gly Arg Ser Pro Leu Asp Pro Met Thr Ser Pro Gly Ser Gly Leu
            100                 105                 110
Ile Leu Gln Ala Asn Phe Val His Ser Gln Arg Arg Glu Ser Phe Leu
        115                 120                 125
Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ser Met Ser Arg
    130                 135                 140
Asn Ser Ser Ile Ala Ser Asp Ile His Gly Asp Asp Leu Ile Val Thr
145                 150                 155                 160
Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Thr Val Arg Asn Asn Phe
                165                 170                 175
Ala Ala Leu Thr Asn Leu Gln Asp Arg Ala Pro Ser Lys Arg Ser Pro
            180                 185                 190
Met Cys Asn Gln Pro Ser Ile Asn Lys Ala Thr Ile Thr Glu Glu Ala
        195                 200                 205
Tyr Gln Lys Leu Ala Ser Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu
    210                 215                 220
Asp Gln Leu Glu Thr Leu Gln Thr Arg His Ser Val Ser Glu Met Ala
225                 230                 235                 240
Ser Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser
                245                 250                 255
Glu Met Ser Arg Ser Gly Asn Gln Val Ser Glu Phe Ile Ser Asn Thr
            260                 265                 270
Phe Leu Asp Lys Gln His Glu Val Glu Ile Pro Ser Pro Thr Gln Lys
        275                 280                 285
Glu Lys Glu Lys Lys Lys Arg Pro Met Ser Gln Ile Ser Gly Val Lys
    290                 295                 300
Lys Leu Met His Ser Ser Ser Leu Thr Asn Ser Ser Ile Pro Arg Phe
305                 310                 315                 320
Gly Val Lys Thr Glu Gln Glu Asp Val Leu Ala Lys Glu Leu Glu Asp
                325                 330                 335
Val Asn Lys Trp Gly Leu His Val Phe Arg Ile Ala Glu Leu Ser Gly
            340                 345                 350
Asn Arg Pro Leu Thr Val Ile Met His Thr Ile Phe Gln Glu Arg Asp
        355                 360                 365
Leu Leu Lys Thr Phe Lys Ile Pro Val Asp Thr Leu Ile Thr Tyr Leu
    370                 375                 380
Met Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr His Asn Asn
385                 390                 395                 400
Ile His Ala Ala Asp Val Val Gln Ser Thr His Val Leu Leu Ser Thr
                405                 410                 415
```

Pro Ala Leu Glu Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile
420 425 430

Phe Ala Ser Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln
435 440 445

Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Ser
450 455 460

Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln
465 470 475 480

Glu Glu Asn Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln
485 490 495

Ser Leu Arg Lys Met Val Ile Asp Ile Val Leu Ala Thr Asp Met Ser
500 505 510

Lys His Met Asn Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys
515 520 525

Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg
530 535 540

Ile Gln Val Leu Gln Asn Met Val His Cys Ala Asp Leu Ser Asn Pro
545 550 555 560

Thr Lys Pro Leu Gln Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu
565 570 575

Glu Phe Phe Arg Gln Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile
580 585 590

Ser Pro Met Cys Asp Lys His Asn Ala Ser Val Glu Lys Ser Gln Val
595 600 605

Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp
610 615 620

Leu Val His Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn
625 630 635 640

Arg Glu Trp Tyr Gln Ser Thr Ile Pro Gln Ser Pro Ser Pro Ala Pro
645 650 655

Asp Asp Pro Glu Glu Gly Arg Gln Gly Gln Thr Glu Lys Phe Gln Phe
660 665 670

Glu Leu Thr Leu Glu Glu Asp Gly Glu Ser Asp Thr Glu Lys Asp Ser
675 680 685

Gly Ser Gln Val Glu Glu Asp Thr Ser Cys Ser Asp Ser Lys Thr Leu
690 695 700

Cys Thr Gln Asp Ser Glu Ser Thr Glu Ile Pro Leu Asp Glu Gln Val
705 710 715 720

Glu Glu Glu Ala Val Gly Glu Glu Glu Glu Ser Gln Pro Glu Ala Cys
725 730 735

Val Ile Asp Asp Arg Ser Pro Asp Thr Thr Gly Ile Leu Gln Ser Thr
740 745 750

Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly
755 760 765

Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly
770 775 780

Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp
785 790 795 800

Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys
805 810 815

Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val
820 825 830

Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe
835 840 845

Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe
    850   855   860
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
865   870   875   880
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
                885   890   895
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
            900   905   910
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
        915   920   925
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
    930   935   940
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
945   950   955   960
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
                965   970   975
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
            980   985   990
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
        995   1000

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3201 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3198
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

ATG GAG GCA GAG GGC AGC AGC GCG CCG GCC CGG GCG GGC AGC GGA GAG 48
Met Glu Ala Glu Gly Ser Ser Ala Pro Ala Arg Ala Gly Ser Gly Glu
 1   5   10   15

GGC AGC GAC AGC GCC GGC GGG GCC ACG CTC AAA GCC CCC AAG CAT CTC 96
Gly Ser Asp Ser Ala Gly Gly Ala Thr Leu Lys Ala Pro Lys His Leu
            20   25   30

TGG AGG CAC GAG CAG CAC CAC CAG TAC CCG CTC CGG CAG CCC CAG TTC 144
Trp Arg His Glu Gln His His Gln Tyr Pro Leu Arg Gln Pro Gln Phe
        35   40   45

CGC CTC CTG CAT CCC CAT CAC CAC CTG CCC CCG CCG CCG CCA CCC TCG 192
Arg Leu Leu His Pro His His His Leu Pro Pro Pro Pro Pro Pro Ser
    50   55   60

```
CCC CAG CCC CAG CCC CAG TGT CCG CTA CAG CCG CCG CCG CCG CCC CCC      240
Pro Gln Pro Gln Pro Gln Cys Pro Leu Gln Pro Pro Pro Pro Pro Pro
65                  70                  75                  80

CTG CCG CCG CCC CCG CCG CCG CCC GGG GCT GCC CGC GGC CGC TAC GCC      288
Leu Pro Pro Pro Pro Pro Pro Pro Gly Ala Ala Arg Gly Arg Tyr Ala
                85                  90                  95

TCG AGC GGG GCC ACC GGC CGC GTC CGG CAT CGC GGC TAC TCG GAC ACC      336
Ser Ser Gly Ala Thr Gly Arg Val Arg His Arg Gly Tyr Ser Asp Thr
            100                 105                 110

GAG CGC TAC CTG TAC TGT CGC GCC ATG GAC CGC ACC TCC TAC GCG GTG      384
Glu Arg Tyr Leu Tyr Cys Arg Ala Met Asp Arg Thr Ser Tyr Ala Val
        115                 120                 125

GAG ACC GGC CAC CGG CCC GGC CTG AAG AAA TCC AGG ATG TCC TGG CCC      432
Glu Thr Gly His Arg Pro Gly Leu Lys Lys Ser Arg Met Ser Trp Pro
    130                 135                 140

TCC TCG TTC CAG GGA CTC AGG CGT TTT GAT GTG GAC AAT GGC ACA TCT      480
Ser Ser Phe Gln Gly Leu Arg Arg Phe Asp Val Asp Asn Gly Thr Ser
145                 150                 155                 160

GCG GGA CGG AGT CCC TTG GAT CCC ATG ACC AGC CCA GGA TCC GGG CTA      528
Ala Gly Arg Ser Pro Leu Asp Pro Met Thr Ser Pro Gly Ser Gly Leu
                165                 170                 175

ATT CTC CAA GCA AAT TTT GTC CAC AGT CAA CGA CGG GAG TCC TTC CTG      576
Ile Leu Gln Ala Asn Phe Val His Ser Gln Arg Arg Glu Ser Phe Leu
            180                 185                 190

TAT CGA TCC GAC AGC GAT TAT GAC CTC TCT CCA AAG TCT ATG TCC CGG      624
Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ser Met Ser Arg
        195                 200                 205

AAC TCC TCC ATT GCC AGT GAT ATA CAC GGA GAT GAC TTG ATT GTG ACT      672
Asn Ser Ser Ile Ala Ser Asp Ile His Gly Asp Asp Leu Ile Val Thr
    210                 215                 220

CCA TTT GCT CAG GTC TTG GCC AGT CTG CGA ACT GTA CGA AAC AAC TTT      720
Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Thr Val Arg Asn Asn Phe
225                 230                 235                 240

GCT GCA TTA ACT AAT TTG CAA GAT CGA GCA CCT AGC AAA AGA TCA CCC      768
Ala Ala Leu Thr Asn Leu Gln Asp Arg Ala Pro Ser Lys Arg Ser Pro
                245                 250                 255

ATG TGC AAC CAA CCA TCC ATC AAC AAA GCC ACC ATA ACA GAG GAG GCC      816
Met Cys Asn Gln Pro Ser Ile Asn Lys Ala Thr Ile Thr Glu Glu Ala
            260                 265                 270

TAC CAG AAA CTG GCC AGC GAG ACC CTG GAG GAG CTG GAC TGG TGT CTG      864
Tyr Gln Lys Leu Ala Ser Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu
```

275 280 285

GAC CAG CTA GAG ACC CTA CAG ACC AGG CAC TCC GTC AGT GAG ATG GCC 912
Asp Gln Leu Glu Thr Leu Gln Thr Arg His Ser Val Ser Glu Met Ala
290 295 300

TCC AAC AAG TTT AAA AGG ATG CTT AAT CGG GAG CTC ACC CAT CTC TCT 960
Ser Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser
305 310 315 320

GAA ATG AGT CGG TCT GGA AAT CAA GTG TCA GAG TTT ATA TCA AAC ACA 1008
Glu Met Ser Arg Ser Gly Asn Gln Val Ser Glu Phe Ile Ser Asn Thr
325 330 335

TTC TTA GAT AAG CAA CAT GAA GTG GAA ATT CCT TCT CCA ACT CAG AAG 1056
Phe Leu Asp Lys Gln His Glu Val Glu Ile Pro Ser Pro Thr Gln Lys
340 345 350

GAA AAG GAG AAA AAG AAA AGA CCA ATG TCT CAG ATC AGT GGA GTC AAG 1104
Glu Lys Glu Lys Lys Lys Arg Pro Met Ser Gln Ile Ser Gly Val Lys
355 360 365

AAA TTG ATG CAC AGC TCT AGT CTG ACT AAT TCA AGT ATC CCA AGG TTT 1152
Lys Leu Met His Ser Ser Ser Leu Thr Asn Ser Ser Ile Pro Arg Phe
370 375 380

GGA GTT AAA ACT GAA CAA GAA GAT GTC CTT GCC AAG GAA CTA GAA GAT 1200
Gly Val Lys Thr Glu Gln Glu Asp Val Leu Ala Lys Glu Leu Glu Asp
385 390 395 400

GTG AAC AAA TGG GGT CTT CAT GTT TTC AGA ATA GCA GAG TTG TCT GGT 1248
Val Asn Lys Trp Gly Leu His Val Phe Arg Ile Ala Glu Leu Ser Gly
405 410 415

AAC CGG CCC TTG ACT GTT ATC ATG CAC ACC ATT TTT CAG GAA CGG GAT 1296
Asn Arg Pro Leu Thr Val Ile Met His Thr Ile Phe Gln Glu Arg Asp
420 425 430

TTA TTA AAA ACA TTT AAA ATT CCA GTA GAT ACT TTA ATT ACA TAT CTT 1344
Leu Leu Lys Thr Phe Lys Ile Pro Val Asp Thr Leu Ile Thr Tyr Leu
435 440 445

ATG ACT CTC GAA GAC CAT TAC CAT GCT GAT GTG GCC TAT CAC AAC AAT 1392
Met Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr His Asn Asn
450 455 460

ATC CAT GCT GCA GAT GTT GTC CAG TCT ACT CAT GTG CTA TTA TCT ACA 1440
Ile His Ala Ala Asp Val Val Gln Ser Thr His Val Leu Leu Ser Thr
465 470 475 480

CCT GCT TTG GAG GCT GTG TTT ACA GAT TTG GAG ATT CTT GCA GCA ATT 1488
Pro Ala Leu Glu Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile
485 490 495

TTT GCC AGT GCA ATA CAT GAT GTA GAT CAT CCT GGT GTG TCC AAT CAA 1536
Phe Ala Ser Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln
500 505 510

TTT CTG ATC AAT ACA AAC TCT GAA CTT GCC TTG ATG TAC AAT GAT TCC 1584
Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Ser
515 520 525

TCA GTC TTA GAG AAC CAT CAT TTG GCT GTG GGC TTT AAA TTG CTT CAG 1632
Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln
530 535 540

GAA GAA AAC TGT GAC ATT TTC CAG AAT TTG ACC AAA AAA CAA AGA CAA 1680
Glu Glu Asn Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln
545 550 555 560

TCT TTA AGG AAA ATG GTC ATT GAC ATC GTA CTT GCA ACA GAT ATG TCA 1728
Ser Leu Arg Lys Met Val Ile Asp Ile Val Leu Ala Thr Asp Met Ser
565 570 575

AAA CAC ATG AAT CTA CTG GCT GAT TTG AAG ACT ATG GTT GAA ACT AAG 1776
Lys His Met Asn Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys
580 585 590

AAA GTG ACA AGC TCT GGA GTT CTT CTT CTT GAT AAT TAT TCC GAT AGG 1824
Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg
595 600 605

ATT CAG GTT CTT CAG AAT ATG GTG CAC TGT GCA GAT CTG AGC AAC CCA 1872
Ile Gln Val Leu Gln Asn Met Val His Cys Ala Asp Leu Ser Asn Pro
610 615 620

ACA AAG CCT CTC CAG CTG TAC CGC CAG TGG ACG GAC CGG ATA ATG GAG 1920
Thr Lys Pro Leu Gln Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu
625 630 635 640

GAG TTC TTC CGC CAA GGA GAC CGA GAG AGG GAA CGT GGC ATG GAG ATA 1968
Glu Phe Phe Arg Gln Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile
645 650 655

AGC CCC ATG TGT GAC AAG CAC AAT GCT TCC GTG GAA AAA TCA CAG GTG 2016
Ser Pro Met Cys Asp Lys His Asn Ala Ser Val Glu Lys Ser Gln Val
660 665 670

GGC TTC ATA GAC TAT ATT GTT CAT CCC CTC TGG GAG ACA TGG GCA GAC 2064
Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp
675 680 685

CTC GTC CAC CCT GAC GCC CAG GAT ATT TTG GAC ACT TTG GAG GAC AAT 2112
Leu Val His Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn
690 695 700

CGT GAA TGG TAC CAG AGC ACA ATC CCT CAG AGC CCC TCT CCT GCA CCT 2160
Arg Glu Trp Tyr Gln Ser Thr Ile Pro Gln Ser Pro Ser Pro Ala Pro

705 710 715 720

GAT GAC CCA GAG GAG GGC CGG CAG GGT CAA ACT GAG AAA TTC CAG TTT 2208

Asp Asp Pro Glu Glu Gly Arg Gln Gly Gln Thr Glu Lys Phe Gln Phe

725 730 735

GAA CTA ACT TTA GAG GAA GAT GGT GAG TCA GAC ACG GAA AAG GAC AGT 2256

Glu Leu Thr Leu Glu Glu Asp Gly Glu Ser Asp Thr Glu Lys Asp Ser

740 745 750

GGC AGT CAA GTG GAA GAA GAC ACT AGC TGC AGT GAC TCC AAG ACT CTT 2304

Gly Ser Gln Val Glu Glu Asp Thr Ser Cys Ser Asp Ser Lys Thr Leu

755 760 765

TGT ACT CAA GAC TCA GAG TCT ACT GAA ATT CCC CTT GAT GAA CAG GTT 2352

Cys Thr Gln Asp Ser Glu Ser Thr Glu Ile Pro Leu Asp Glu Gln Val

770 775 780

GAA GAG GAG GCA GTA GGG GAA GAA GAG GAA AGC CAG CCT GAA GCC TGT 2400

Glu Glu Glu Ala Val Gly Glu Glu Glu Glu Ser Gln Pro Glu Ala Cys

785 790 795 800

GTC ATA GAT GAT CGT TCT CCT GAC ACG ACG GGA ATT CTG CAG TCG ACG 2448

Val Ile Asp Asp Arg Ser Pro Asp Thr Thr Gly Ile Leu Gln Ser Thr

805 810 815

GTA CCG CGG GCC CGG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC 2496

Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly

820 825 830

GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC 2544

Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly

835 840 845

GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT 2592

Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp

850 855 860

GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG 2640

Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys

865 870 875 880

CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG 2688

Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val

885 890 895

CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC 2736

Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe

900 905 910

AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC 2784

Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe

915 920 925

AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC 2832
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
930 935 940

GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG 2880
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
945 950 955 960

GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC 2928
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
965 970 975

AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC 2976
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
980 985 990

TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC 3024
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
995 1000 1005

CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC 3072
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
1010 1015 1020

GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC 3120
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
1025 1030 1035 1040

GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG 3168
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
1045 1050 1055

ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 3201
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
1060 1065

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1066 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Met Glu Ala Glu Gly Ser Ser Ala Pro Ala Arg Ala Gly Ser Gly Glu
1 5 10 15
Gly Ser Asp Ser Ala Gly Gly Ala Thr Leu Lys Ala Pro Lys His Leu
20 25 30

Trp Arg His Glu Gln His His Gln Tyr Pro Leu Arg Gln Pro Gln Phe
35 40 45

Arg Leu Leu His Pro His His His Leu Pro Pro Pro Pro Pro Pro Ser
50 55 60

Pro Gln Pro Gln Pro Gln Cys Pro Leu Gln Pro Pro Pro Pro Pro Pro
65 70 75 80

Leu Pro Pro Pro Pro Pro Pro Pro Gly Ala Ala Arg Gly Arg Tyr Ala
85 90 95

Ser Ser Gly Ala Thr Gly Arg Val Arg His Arg Gly Tyr Ser Asp Thr
100 105 110

Glu Arg Tyr Leu Tyr Cys Arg Ala Met Asp Arg Thr Ser Tyr Ala Val
115 120 125

Glu Thr Gly His Arg Pro Gly Leu Lys Lys Ser Arg Met Ser Trp Pro
130 135 140

Ser Ser Phe Gln Gly Leu Arg Arg Phe Asp Val Asp Asn Gly Thr Ser
145 150 155 160

Ala Gly Arg Ser Pro Leu Asp Pro Met Thr Ser Pro Gly Ser Gly Leu
165 170 175

Ile Leu Gln Ala Asn Phe Val His Ser Gln Arg Arg Glu Ser Phe Leu
180 185 190

Tyr Arg Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ser Met Ser Arg
195 200 205

Asn Ser Ser Ile Ala Ser Asp Ile His Gly Asp Asp Leu Ile Val Thr
210 215 220

Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Thr Val Arg Asn Asn Phe
225 230 235 240

Ala Ala Leu Thr Asn Leu Gln Asp Arg Ala Pro Ser Lys Arg Ser Pro
245 250 255

Met Cys Asn Gln Pro Ser Ile Asn Lys Ala Thr Ile Thr Glu Glu Ala
260 265 270

Tyr Gln Lys Leu Ala Ser Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu
275 280 285

Asp Gln Leu Glu Thr Leu Gln Thr Arg His Ser Val Ser Glu Met Ala
290 295 300

Ser Asn Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser
305 310 315 320

Glu Met Ser Arg Ser Gly Asn Gln Val Ser Glu Phe Ile Ser Asn Thr
325 330 335

Phe Leu Asp Lys Gln His Glu Val Glu Ile Pro Ser Pro Thr Gln Lys
340 345 350

Glu Lys Glu Lys Lys Lys Arg Pro Met Ser Gln Ile Ser Gly Val Lys
355 360 365

Lys Leu Met His Ser Ser Ser Leu Thr Asn Ser Ser Ile Pro Arg Phe
370 375 380

Gly Val Lys Thr Glu Gln Glu Asp Val Leu Ala Lys Glu Leu Glu Asp
385 390 395 400

Val Asn Lys Trp Gly Leu His Val Phe Arg Ile Ala Glu Leu Ser Gly
405 410 415

Asn Arg Pro Leu Thr Val Ile Met His Thr Ile Phe Gln Glu Arg Asp
420 425 430

Leu Leu Lys Thr Phe Lys Ile Pro Val Asp Thr Leu Ile Thr Tyr Leu
435 440 445

Met Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr His Asn Asn
450 455 460

Ile His Ala Ala Asp Val Val Gln Ser Thr His Val Leu Leu Ser Thr
465 470 475 480
Pro Ala Leu Glu Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile
485 490 495
Phe Ala Ser Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln
500 505 510
Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Ser
515 520 525
Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln
530 535 540
Glu Glu Asn Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln
545 550 555 560
Ser Leu Arg Lys Met Val Ile Asp Ile Val Leu Ala Thr Asp Met Ser
565 570 575
Lys His Met Asn Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys
580 585 590
Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser Asp Arg
595 600 605
Ile Gln Val Leu Gln Asn Met Val His Cys Ala Asp Leu Ser Asn Pro
610 615 620
Thr Lys Pro Leu Gln Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu
625 630 635 640
Glu Phe Phe Arg Gln Gly Asp Arg Glu Arg Glu Arg Gly Met Glu Ile
645 650 655
Ser Pro Met Cys Asp Lys His Asn Ala Ser Val Glu Lys Ser Gln Val
660 665 670
Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp
675 680 685
Leu Val His Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn
690 695 700
Arg Glu Trp Tyr Gln Ser Thr Ile Pro Gln Ser Pro Ser Pro Ala Pro
705 710 715 720
Asp Asp Pro Glu Glu Gly Arg Gln Gly Gln Thr Glu Lys Phe Gln Phe
725 730 735
Glu Leu Thr Leu Glu Glu Asp Gly Glu Ser Asp Thr Glu Lys Asp Ser
740 745 750
Gly Ser Gln Val Glu Glu Asp Thr Ser Cys Ser Asp Ser Lys Thr Leu
755 760 765
Cys Thr Gln Asp Ser Glu Ser Thr Glu Ile Pro Leu Asp Glu Gln Val
770 775 780
Glu Glu Glu Ala Val Gly Glu Glu Glu Glu Ser Gln Pro Glu Ala Cys
785 790 795 800
Val Ile Asp Asp Arg Ser Pro Asp Thr Thr Gly Ile Leu Gln Ser Thr
805 810 815
Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly
820 825 830
Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly
835 840 845
Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp
850 855 860
Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys
865 870 875 880
Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val
885 890 895

Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe
900 905 910
Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe
915 920 925
Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly
930 935 940
Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu
945 950 955 960
Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His
965 970 975
Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn
980 985 990
Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp
995 1000 1005
His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro
1010 1015 1020
Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn
025 1030 1035 1040
Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly
1045 1050 1055
Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
1060 1065

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3024 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...3021
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

ATG AGC TGG TCA CCT TCC CTG ACA ACG CAG ACA TGT GGG GCC TGG GAA 48
Met Ser Trp Ser Pro Ser Leu Thr Thr Gln Thr Cys Gly Ala Trp Glu
1 5 10 15

ATG AAA GAG CGC CTT GGG ACA GGG GGA TTT GGA AAT GTC ATC CGA TGG 96
Met Lys Glu Arg Leu Gly Thr Gly Gly Phe Gly Asn Val Ile Arg Trp
20 25 30

CAC AAT CAG GAA ACA GGT GAG CAG ATT GCC ATC AAG CAG TGC CGG CAG 144
His Asn Gln Glu Thr Gly Glu Gln Ile Ala Ile Lys Gln Cys Arg Gln
35 40 45

GAG CTC AGC CCC CGG AAC CGA GAG CGG TGG TGC CTG GAG ATC CAG ATC 192
Glu Leu Ser Pro Arg Asn Arg Glu Arg Trp Cys Leu Glu Ile Gln Ile

50 55 60

ATG AGA AGG CTG ACC CAC CCC AAT GTG GTG GCT GCC CGA GAT GTC CCT 240
Met Arg Arg Leu Thr His Pro Asn Val Val Ala Ala Arg Asp Val Pro
65 70 75 80

GAG GGG ATG CAG AAC TTG GCG CCC AAT GAC CTG CCC CTG CTG GCC ATG 288
Glu Gly Met Gln Asn Leu Ala Pro Asn Asp Leu Pro Leu Leu Ala Met
85 90 95

GAG TAC TGC CAA GGA GGA GAT CTC CGG AAG TAC CTG AAC CAG TTT GAG 336
Glu Tyr Cys Gln Gly Gly Asp Leu Arg Lys Tyr Leu Asn Gln Phe Glu
100 105 110

AAC TGC TGT GGT CTG CGG GAA GGT GCC ATC CTC ACC TTG CTG AGT GAC 384
Asn Cys Cys Gly Leu Arg Glu Gly Ala Ile Leu Thr Leu Leu Ser Asp
115 120 125

ATT GCC TCT GCG CTT AGA TAC CTT CAT GAA AAC AGA ATC ATC CAT CGG 432
Ile Ala Ser Ala Leu Arg Tyr Leu His Glu Asn Arg Ile Ile His Arg
130 135 140

GAT CTA AAG CCA GAA AAC ATC GTC CTG CAG CAA GGA GAA CAG AGG TTA 480
Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Gln Gly Glu Gln Arg Leu
145 150 155 160

ATA CAC AAA ATT ATT GAC CTA GGA TAT GCC AAG GAG CTG GAT CAG GGC 528
Ile His Lys Ile Ile Asp Leu Gly Tyr Ala Lys Glu Leu Asp Gln Gly
165 170 175

AGT CTT TGC ACA TCA TTC GTG GGG ACC CTG CAG TAC CTG GCC CCA GAG 576
Ser Leu Cys Thr Ser Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu
180 185 190

CTA CTG GAG CAG CAG AAG TAC ACA GTG ACC GTC GAC TAC TGG AGC TTC 624
Leu Leu Glu Gln Gln Lys Tyr Thr Val Thr Val Asp Tyr Trp Ser Phe
195 200 205

GGC ACC CTG GCC TTT GAG TGC ATC ACG GGC TTC CGG CCC TTC CTC CCC 672
Gly Thr Leu Ala Phe Glu Cys Ile Thr Gly Phe Arg Pro Phe Leu Pro
210 215 220

AAC TGG CAG CCC GTG CAG TGG CAT TCA AAA GTG CGG CAG AAG AGT GAG 720
Asn Trp Gln Pro Val Gln Trp His Ser Lys Val Arg Gln Lys Ser Glu
225 230 235 240

GTG GAC ATT GTT GTT AGC GAA GAC TTG AAT GGA ACG GTG AAG TTT TCA 768
Val Asp Ile Val Val Ser Glu Asp Leu Asn Gly Thr Val Lys Phe Ser
245 250 255

AGC TCT TTA CCC TAC CCC AAT AAT CTT AAC AGT GTC CTG GCT GAG CGA 816
Ser Ser Leu Pro Tyr Pro Asn Asn Leu Asn Ser Val Leu Ala Glu Arg
260 265 270

```
CTG GAG AAG TGG CTG CAA CTG ATG CTG ATG TGG CAC CCC CGA CAG AGG      864
Leu Glu Lys Trp Leu Gln Leu Met Leu Met Trp His Pro Arg Gln Arg
        275                 280                 285

GGC ACG GAT CCC ACG TAT GGG CCC AAT GGC TGC TTC AAG GCC CTG GAT      912
Gly Thr Asp Pro Thr Tyr Gly Pro Asn Gly Cys Phe Lys Ala Leu Asp
    290                 295                 300

GAC ATC TTA AAC TTA AAG CTG GTT CAT ATC TTG AAC ATG GTC ACG GGC      960
Asp Ile Leu Asn Leu Lys Leu Val His Ile Leu Asn Met Val Thr Gly
305                 310                 315                 320

ACC ATC CAC ACC TAC CCT GTG ACA GAG GAT GAG AGT CTG CAG AGC TTG     1008
Thr Ile His Thr Tyr Pro Val Thr Glu Asp Glu Ser Leu Gln Ser Leu
                325                 330                 335

AAG GCC AGA ATC CAA CAG GAC ACG GGC ATC CCA GAG GAG GAC CAG GAG     1056
Lys Ala Arg Ile Gln Gln Asp Thr Gly Ile Pro Glu Glu Asp Gln Glu
            340                 345                 350

CTG CTG CAG GAA GCG GGC CTG GCG TTG ATC CCC GAT AAG CCT GCC ACT     1104
Leu Leu Gln Glu Ala Gly Leu Ala Leu Ile Pro Asp Lys Pro Ala Thr
        355                 360                 365

CAG TGT ATT TCA GAC GGC AAG TTA AAT GAG GGC CAC ACA TTG GAC ATG     1152
Gln Cys Ile Ser Asp Gly Lys Leu Asn Glu Gly His Thr Leu Asp Met
    370                 375                 380

GAT CTT GTT TTT CTC TTT GAC AAC AGT AAA ATC ACC TAT GAG ACT CAG     1200
Asp Leu Val Phe Leu Phe Asp Asn Ser Lys Ile Thr Tyr Glu Thr Gln
385                 390                 395                 400

ATC TCC CCA CGG CCC CAA CCT GAA AGT GTC AGC TGT ATC CTT CAA GAG     1248
Ile Ser Pro Arg Pro Gln Pro Glu Ser Val Ser Cys Ile Leu Gln Glu
                405                 410                 415

CCC AAG AGG AAT CTC GCC TTC TTC CAG CTG AGG AAG GTG TGG GGC CAG     1296
Pro Lys Arg Asn Leu Ala Phe Phe Gln Leu Arg Lys Val Trp Gly Gln
            420                 425                 430

GTC TGG CAC AGC ATC CAG ACC CTG AAG GAA GAT TGC AAC CGG CTG CAG     1344
Val Trp His Ser Ile Gln Thr Leu Lys Glu Asp Cys Asn Arg Leu Gln
        435                 440                 445

CAG GGA CAG CGA GCC GCC ATG ATG AAT CTC CTC CGA AAC AAC AGC TGC     1392
Gln Gly Gln Arg Ala Ala Met Met Asn Leu Leu Arg Asn Asn Ser Cys
    450                 455                 460

CTC TCC AAA ATG AAG AAT TCC ATG GCT TCC ATG TCT CAG CAG CTC AAG     1440
Leu Ser Lys Met Lys Asn Ser Met Ala Ser Met Ser Gln Gln Leu Lys
465                 470                 475                 480

GCC AAG TTG GAT TTC TTC AAA ACC AGC ATC CAG ATT GAC CTG GAG AAG     1488
Ala Lys Leu Asp Phe Phe Lys Thr Ser Ile Gln Ile Asp Leu Glu Lys
```

485 490 495

TAC AGC GAG CAA ACC GAG TTT GGG ATC ACA TCA GAT AAA CTG CTG CTG 1536
Tyr Ser Glu Gln Thr Glu Phe Gly Ile Thr Ser Asp Lys Leu Leu Leu
500 505 510

GCC TGG AGG GAA ATG GAG CAG GCT GTG GAG CTC TGT GGG CGG GAG AAC 1584
Ala Trp Arg Glu Met Glu Gln Ala Val Glu Leu Cys Gly Arg Glu Asn
515 520 525

GAA GTG AAA CTC CTG GTA GAA CGG ATG ATG GCT CTG CAG ACC GAC ATT 1632
Glu Val Lys Leu Leu Val Glu Arg Met Met Ala Leu Gln Thr Asp Ile
530 535 540

GTG GAC TTA CAG AGG AGC CCC ATG GGC CGG AAG CAG GGG GGA ACG CTG 1680
Val Asp Leu Gln Arg Ser Pro Met Gly Arg Lys Gln Gly Gly Thr Leu
545 550 555 560

GAC GAC CTA GAG GAG CAA GCA AGG GAG CTG TAC AGG AGA CTA AGG GAA 1728
Asp Asp Leu Glu Glu Gln Ala Arg Glu Leu Tyr Arg Arg Leu Arg Glu
565 570 575

AAA CCT CGA GAC CAG CGA ACT GAG GGT GAC AGT CAG GAA ATG GTA CGG 1776
Lys Pro Arg Asp Gln Arg Thr Glu Gly Asp Ser Gln Glu Met Val Arg
580 585 590

CTG CTG CTT CAG GCA ATT CAG AGC TTC GAG AAG AAA GTG CGA GTG ATC 1824
Leu Leu Leu Gln Ala Ile Gln Ser Phe Glu Lys Lys Val Arg Val Ile
595 600 605

TAT ACG CAG CTC AGT AAA ACT GTG GTT TGC AAG CAG AAG GCG CTG GAA 1872
Tyr Thr Gln Leu Ser Lys Thr Val Val Cys Lys Gln Lys Ala Leu Glu
610 615 620

CTG TTG CCC AAG GTG GAA GAG GTG GTG AGC TTA ATG AAT GAG GAT GAG 1920
Leu Leu Pro Lys Val Glu Glu Val Val Ser Leu Met Asn Glu Asp Glu
625 630 635 640

AAG ACT GTT GTC CGG CTG CAG GAG AAG CGG CAG AAG GAG CTC TGG AAT 1968
Lys Thr Val Val Arg Leu Gln Glu Lys Arg Gln Lys Glu Leu Trp Asn
645 650 655

CTC CTG AAG ATT GCT TGT AGC AAG GTC CGT GGT CCT GTC AGT GGA AGC 2016
Leu Leu Lys Ile Ala Cys Ser Lys Val Arg Gly Pro Val Ser Gly Ser
660 665 670

CCG GAT AGC ATG AAT GCC TCT CGA CTT AGC CAG CCT GGG CAG CTG ATG 2064
Pro Asp Ser Met Asn Ala Ser Arg Leu Ser Gln Pro Gly Gln Leu Met
675 680 685

TCT CAG CCC TCC ACG GCC TCC AAC AGC TTA CCT GAG CCA GCC AAG AAG 2112
Ser Gln Pro Ser Thr Ala Ser Asn Ser Leu Pro Glu Pro Ala Lys Lys
690 695 700

AGT GAA GAA CTG GTG GCT GAA GCA CAT AAC CTC TGC ACC CTG CTA GAA 2160
Ser Glu Glu Leu Val Ala Glu Ala His Asn Leu Cys Thr Leu Leu Glu
705 710 715 720

AAT GCC ATA CAG GAC ACT GTG AGG GAA CAA GAC CAG AGT TTC ACG GCC 2208
Asn Ala Ile Gln Asp Thr Val Arg Glu Gln Asp Gln Ser Phe Thr Ala
725 730 735

CTA GAC TGG AGC TGG TTA CAG ACG GAA GAA GAA GAG CAC AGC TGC CTG 2256
Leu Asp Trp Ser Trp Leu Gln Thr Glu Glu Glu Glu His Ser Cys Leu
740 745 750

GAG CAG GCC TCA TGG GTA CCG CGG GCC CGG GAT CCA CCG GTC GCC ACC 2304
Glu Gln Ala Ser Trp Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr
755 760 765

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 2352
Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
770 775 780

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 2400
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
785 790 795 800

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 2448
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
805 810 815

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 2496
Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
820 825 830

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 2544
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
835 840 845

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 2592
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
850 855 860

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 2640
Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
865 870 875 880

GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 2688
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
885 890 895

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 2736
Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
900 905 910

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 2784
Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn

915 920 925

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 2832
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
930 935 940

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 2880
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
945 950 955 960

CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG 2928
Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
965 970 975

AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 2976
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
980 985 990

GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 3024
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
995 1000 1005

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1007 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Met Ser Trp Ser Pro Ser Leu Thr Thr Gln Thr Cys Gly Ala Trp Glu
1 5 10 15
Met Lys Glu Arg Leu Gly Thr Gly Gly Phe Gly Asn Val Ile Arg Trp
20 25 30
His Asn Gln Glu Thr Gly Glu Gln Ile Ala Ile Lys Gln Cys Arg Gln
35 40 45
Glu Leu Ser Pro Arg Asn Arg Glu Arg Trp Cys Leu Glu Ile Gln Ile
50 55 60
Met Arg Arg Leu Thr His Pro Asn Val Val Ala Ala Arg Asp Val Pro
65 70 75 80
Glu Gly Met Gln Asn Leu Ala Pro Asn Asp Leu Pro Leu Leu Ala Met
85 90 95
Glu Tyr Cys Gln Gly Gly Asp Leu Arg Lys Tyr Leu Asn Gln Phe Glu
100 105 110
Asn Cys Cys Gly Leu Arg Glu Gly Ala Ile Leu Thr Leu Leu Ser Asp
115 120 125
Ile Ala Ser Ala Leu Arg Tyr Leu His Glu Asn Arg Ile Ile His Arg
130 135 140

Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Gln Gly Glu Gln Arg Leu
145 150 155 160
Ile His Lys Ile Ile Asp Leu Gly Tyr Ala Lys Glu Leu Asp Gln Gly
165 170 175
Ser Leu Cys Thr Ser Phe Val Gly Thr Leu Gln Tyr Leu Ala Pro Glu
180 185 190
Leu Leu Glu Gln Gln Lys Tyr Thr Val Thr Val Asp Tyr Trp Ser Phe
195 200 205
Gly Thr Leu Ala Phe Glu Cys Ile Thr Gly Phe Arg Pro Phe Leu Pro
210 215 220
Asn Trp Gln Pro Val Gln Trp His Ser Lys Val Arg Gln Lys Ser Glu
225 230 235 240
Val Asp Ile Val Val Ser Glu Asp Leu Asn Gly Thr Val Lys Phe Ser
245 250 255
Ser Ser Leu Pro Tyr Pro Asn Asn Leu Asn Ser Val Leu Ala Glu Arg
260 265 270
Leu Glu Lys Trp Leu Gln Leu Met Leu Met Trp His Pro Arg Gln Arg
275 280 285
Gly Thr Asp Pro Thr Tyr Gly Pro Asn Gly Cys Phe Lys Ala Leu Asp
290 295 300
Asp Ile Leu Asn Leu Lys Leu Val His Ile Leu Asn Met Val Thr Gly
305 310 315 320
Thr Ile His Thr Tyr Pro Val Thr Glu Asp Glu Ser Leu Gln Ser Leu
325 330 335
Lys Ala Arg Ile Gln Gln Asp Thr Gly Ile Pro Glu Glu Asp Gln Glu
340 345 350
Leu Leu Gln Glu Ala Gly Leu Ala Leu Ile Pro Asp Lys Pro Ala Thr
355 360 365
Gln Cys Ile Ser Asp Gly Lys Leu Asn Glu Gly His Thr Leu Asp Met
370 375 380
Asp Leu Val Phe Leu Phe Asp Asn Ser Lys Ile Thr Tyr Glu Thr Gln
385 390 395 400
Ile Ser Pro Arg Pro Gln Pro Glu Ser Val Ser Cys Ile Leu Gln Glu
405 410 415
Pro Lys Arg Asn Leu Ala Phe Phe Gln Leu Arg Lys Val Trp Gly Gln
420 425 430
Val Trp His Ser Ile Gln Thr Leu Lys Glu Asp Cys Asn Arg Leu Gln
435 440 445
Gln Gly Gln Arg Ala Ala Met Met Asn Leu Leu Arg Asn Asn Ser Cys
450 455 460
Leu Ser Lys Met Lys Asn Ser Met Ala Ser Met Ser Gln Gln Leu Lys
465 470 475 480
Ala Lys Leu Asp Phe Phe Lys Thr Ser Ile Gln Ile Asp Leu Glu Lys
485 490 495
Tyr Ser Glu Gln Thr Glu Phe Gly Ile Thr Ser Asp Lys Leu Leu Leu
500 505 510
Ala Trp Arg Glu Met Glu Gln Ala Val Glu Leu Cys Gly Arg Glu Asn
515 520 525
Glu Val Lys Leu Leu Val Glu Arg Met Met Ala Leu Gln Thr Asp Ile
530 535 540
Val Asp Leu Gln Arg Ser Pro Met Gly Arg Lys Gln Gly Gly Thr Leu
545 550 555 560
Asp Asp Leu Glu Glu Gln Ala Arg Glu Leu Tyr Arg Arg Leu Arg Glu
565 570 575

Lys Pro Arg Asp Gln Arg Thr Glu Gly Asp Ser Gln Glu Met Val Arg
580 585 590

Leu Leu Leu Gln Ala Ile Gln Ser Phe Glu Lys Lys Val Arg Val Ile
595 600 605

Tyr Thr Gln Leu Ser Lys Thr Val Val Cys Lys Gln Lys Ala Leu Glu
610 615 620

Leu Leu Pro Lys Val Glu Glu Val Val Ser Leu Met Asn Glu Asp Glu
625 630 635 640

Lys Thr Val Val Arg Leu Gln Glu Lys Arg Gln Lys Glu Leu Trp Asn
645 650 655

Leu Leu Lys Ile Ala Cys Ser Lys Val Arg Gly Pro Val Ser Gly Ser
660 665 670

Pro Asp Ser Met Asn Ala Ser Arg Leu Ser Gln Pro Gly Gln Leu Met
675 680 685

Ser Gln Pro Ser Thr Ala Ser Asn Ser Leu Pro Glu Pro Ala Lys Lys
690 695 700

Ser Glu Glu Leu Val Ala Glu Ala His Asn Leu Cys Thr Leu Leu Glu
705 710 715 720

Asn Ala Ile Gln Asp Thr Val Arg Glu Gln Asp Gln Ser Phe Thr Ala
725 730 735

Leu Asp Trp Ser Trp Leu Gln Thr Glu Glu Glu Glu His Ser Cys Leu
740 745 750

Glu Gln Ala Ser Trp Val Pro Arg Ala Arg Asp Pro Pro Val Ala Thr
755 760 765

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
770 775 780

Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
785 790 795 800

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
805 810 815

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
820 825 830

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
835 840 845

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
850 855 860

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
865 870 875 880

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
885 890 895

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
900 905 910

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
915 920 925

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
930 935 940

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
945 950 955 960

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
965 970 975

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
980 985 990

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
995 1000 1005

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2793 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...2790
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

```
ATG ATG CAC GTG AAT AAT TTT CCC TTT AGA AGG CAT TCC TGG ATA TGT       48
Met Met His Val Asn Asn Phe Pro Phe Arg Arg His Ser Trp Ile Cys
 1               5                  10                  15

TTT GAT GTG GAC AAT GGC ACA TCT GCG GGA CGG AGT CCC TTG GAT CCC       96
Phe Asp Val Asp Asn Gly Thr Ser Ala Gly Arg Ser Pro Leu Asp Pro
            20                  25                  30

ATG ACC AGC CCA GGA TCC GGG CTA ATT CTC CAA GCA AAT TTT GTC CAC      144
Met Thr Ser Pro Gly Ser Gly Leu Ile Leu Gln Ala Asn Phe Val His
        35                  40                  45

AGT CAA CGA CGG GAG TCC TTC CTG TAT CGA TCC GAC AGC GAT TAT GAC      192
Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp
    50                  55                  60

CTC TCT CCA AAG TCT ATG TCC CGG AAC TCC TCC ATT GCC AGT GAT ATA      240
Leu Ser Pro Lys Ser Met Ser Arg Asn Ser Ser Ile Ala Ser Asp Ile
65                  70                  75                  80

CAC GGA GAT GAC TTG ATT GTG ACT CCA TTT GCT CAG GTC TTG GCC AGT      288
His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser
                85                  90                  95

CTG CGA ACT GTA CGA AAC AAC TTT GCT GCA TTA ACT AAT TTG CAA GAT      336
Leu Arg Thr Val Arg Asn Asn Phe Ala Ala Leu Thr Asn Leu Gln Asp
            100                 105                 110

CGA GCA CCT AGC AAA AGA TCA CCC ATG TGC AAC CAA CCA TCC ATC AAC      384
Arg Ala Pro Ser Lys Arg Ser Pro Met Cys Asn Gln Pro Ser Ile Asn
        115                 120                 125

AAA GCC ACC ATA ACA GAG GAG GCC TAC CAG AAA CTG GCC AGC GAG ACC      432
Lys Ala Thr Ile Thr Glu Glu Ala Tyr Gln Lys Leu Ala Ser Glu Thr
    130                 135                 140
```

```
CTG GAG GAG CTG GAC TGG TGT CTG GAC CAG CTA GAG ACC CTA CAG ACC      480
Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Leu Gln Thr
145                 150                 155                 160

AGG CAC TCC GTC AGT GAG ATG GCC TCC AAC AAG TTT AAA AGG ATG CTT      528
Arg His Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu
                165                 170                 175

AAT CGG GAG CTC ACC CAT CTC TCT GAA ATG AGT CGG TCT GGA AAT CAA      576
Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln
            180                 185                 190

GTG TCA GAG TTT ATA TCA AAC ACA TTC TTA GAT AAG CAA CAT GAA GTG      624
Val Ser Glu Phe Ile Ser Asn Thr Phe Leu Asp Lys Gln His Glu Val
        195                 200                 205

GAA ATT CCT TCT CCA ACT CAG AAG GAA AAG GAG AAA AAG AAA AGA CCA      672
Glu Ile Pro Ser Pro Thr Gln Lys Glu Lys Glu Lys Lys Lys Arg Pro
    210                 215                 220

ATG TCT CAG ATC AGT GGA GTC AAG AAA TTG ATG CAC AGC TCT AGT CTG      720
Met Ser Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
225                 230                 235                 240

ACT AAT TCA AGT ATC CCA AGG TTT GGA GTT AAA ACT GAA CAA GAA GAT      768
Thr Asn Ser Ser Ile Pro Arg Phe Gly Val Lys Thr Glu Gln Glu Asp
                245                 250                 255

GTC CTT GCC AAG GAA CTA GAA GAT GTG AAC AAA TGG GGT CTT CAT GTT      816
Val Leu Ala Lys Glu Leu Glu Asp Val Asn Lys Trp Gly Leu His Val
            260                 265                 270

TTC AGA ATA GCA GAG TTG TCT GGT AAC CGG CCC TTG ACT GTT ATC ATG      864
Phe Arg Ile Ala Glu Leu Ser Gly Asn Arg Pro Leu Thr Val Ile Met
        275                 280                 285

CAC ACC ATT TTT CAG GAA CGG GAT TTA TTA AAA ACA TTT AAA ATT CCA      912
His Thr Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Pro
    290                 295                 300

GTA GAT ACT TTA ATT ACA TAT CTT ATG ACT CTC GAA GAC CAT TAC CAT      960
Val Asp Thr Leu Ile Thr Tyr Leu Met Thr Leu Glu Asp His Tyr His
305                 310                 315                 320

GCT GAT GTG GCC TAT CAC AAC AAT ATC CAT GCT GCA GAT GTT GTC CAG     1008
Ala Asp Val Ala Tyr His Asn Asn Ile His Ala Ala Asp Val Val Gln
                325                 330                 335

TCT ACT CAT GTG CTA TTA TCT ACA CCT GCT TTG GAG GCT GTG TTT ACA     1056
Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Glu Ala Val Phe Thr
            340                 345                 350

GAT TTG GAG ATT CTT GCA GCA ATT TTT GCC AGT GCA ATA CAT GAT GTA     1104
Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ser Ala Ile His Asp Val
```

355 360 365

GAT CAT CCT GGT GTG TCC AAT CAA TTT CTG ATC AAT ACA AAC TCT GAA 1152
Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
370 375 380

CTT GCC TTG ATG TAC AAT GAT TCC TCA GTC TTA GAG AAC CAT CAT TTG 1200
Leu Ala Leu Met Tyr Asn Asp Ser Ser Val Leu Glu Asn His His Leu
385 390 395 400

GCT GTG GGC TTT AAA TTG CTT CAG GAA GAA AAC TGT GAC ATT TTC CAG 1248
Ala Val Gly Phe Lys Leu Leu Gln Glu Glu Asn Cys Asp Ile Phe Gln
405 410 415

AAT TTG ACC AAA AAA CAA AGA CAA TCT TTA AGG AAA ATG GTC ATT GAC 1296
Asn Leu Thr Lys Lys Gln Arg Gln Ser Leu Arg Lys Met Val Ile Asp
420 425 430

ATC GTA CTT GCA ACA GAT ATG TCA AAA CAC ATG AAT CTA CTG GCT GAT 1344
Ile Val Leu Ala Thr Asp Met Ser Lys His Met Asn Leu Leu Ala Asp
435 440 445

TTG AAG ACT ATG GTT GAA ACT AAG AAA GTG ACA AGC TCT GGA GTT CTT 1392
Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
450 455 460

CTT CTT GAT AAT TAT TCC GAT AGG ATT CAG GTT CTT CAG AAT ATG GTG 1440
Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Gln Asn Met Val
465 470 475 480

CAC TGT GCA GAT CTG AGC AAC CCA ACA AAG CCT CTC CAG CTG TAC CGC 1488
His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Gln Leu Tyr Arg
485 490 495

CAG TGG ACG GAC CGG ATA ATG GAG GAG TTC TTC CGC CAA GGA GAC CGA 1536
Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Arg Gln Gly Asp Arg
500 505 510

GAG AGG GAA CGT GGC ATG GAG ATA AGC CCC ATG TGT GAC AAG CAC AAT 1584
Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Asn
515 520 525

GCT TCC GTG GAA AAA TCA CAG GTG GGC TTC ATA GAC TAT ATT GTT CAT 1632
Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
530 535 540

CCC CTC TGG GAG ACA TGG GCA GAC CTC GTC CAC CCT GAC GCC CAG GAT 1680
Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp Ala Gln Asp
545 550 555 560

ATT TTG GAC ACT TTG GAG GAC AAT CGT GAA TGG TAC CAG AGC ACA ATC 1728
Ile Leu Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr Gln Ser Thr Ile
565 570 575

CCT CAG AGC CCC TCT CCT GCA CCT GAT GAC CCA GAG GAG GGC CGG CAG 1776
Pro Gln Ser Pro Ser Pro Ala Pro Asp Asp Pro Glu Glu Gly Arg Gln
580 585 590

GGT CAA ACT GAG AAA TTC CAG TTT GAA CTA ACT TTA GAG GAA GAT GGT 1824
Gly Gln Thr Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Asp Gly
595 600 605

GAG TCA GAC ACG GAA AAG GAC AGT GGC AGT CAA GTG GAA GAA GAC ACT 1872
Glu Ser Asp Thr Glu Lys Asp Ser Gly Ser Gln Val Glu Glu Asp Thr
610 615 620

AGC TGC AGT GAC TCC AAG ACT CTT TGT ACT CAA GAC TCA GAG TCT ACT 1920
Ser Cys Ser Asp Ser Lys Thr Leu Cys Thr Gln Asp Ser Glu Ser Thr
625 630 635 640

GAA ATT CCC CTT GAT GAA CAG GTT GAA GAG GAG GCA GTA GGG GAA GAA 1968
Glu Ile Pro Leu Asp Glu Gln Val Glu Glu Glu Ala Val Gly Glu Glu
645 650 655

GAG GAA AGC CAG CCT GAA GCC TGT GTC ATA GAT GAT CGT TCT CCT GAC 2016
Glu Glu Ser Gln Pro Glu Ala Cys Val Ile Asp Asp Arg Ser Pro Asp
660 665 670

ACG ACG GGA ATT CTG CAG TCG ACG GTA CCG CGG GCC CGG GAT CCA CCG 2064
Thr Thr Gly Ile Leu Gln Ser Thr Val Pro Arg Ala Arg Asp Pro Pro
675 680 685

GTC GCC ACC ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG 2112
Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val
690 695 700

CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC 2160
Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser
705 710 715 720

GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG 2208
Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu
725 730 735

AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC 2256
Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu
740 745 750

GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC 2304
Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp
755 760 765

CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC 2352
His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr
770 775 780

GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC 2400
Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr

```
785                 790                 795                 800

CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG     2448
Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu
                805                 810                 815

CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG     2496
Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys
            820                 825                 830

CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG     2544
Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys
        835                 840                 845

CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG     2592
Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu
    850                 855                 860

GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC     2640
Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile
865                 870                 875                 880

GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG     2688
Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln
                885                 890                 895

TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG     2736
Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu
            900                 905                 910

CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG     2784
Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu
        915                 920                 925

TAC AAG TAA                                                         2793
Tyr Lys
    930
```

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 930 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

```
Met Met His Val Asn Asn Phe Pro Phe Arg Arg His Ser Trp Ile Cys
 1               5                  10                  15
```

Phe Asp Val Asp Asn Gly Thr Ser Ala Gly Arg Ser Pro Leu Asp Pro
20 25 30

Met Thr Ser Pro Gly Ser Gly Leu Ile Leu Gln Ala Asn Phe Val His
35 40 45

Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp
50 55 60

Leu Ser Pro Lys Ser Met Ser Arg Asn Ser Ser Ile Ala Ser Asp Ile
65 70 75 80

His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser
85 90 95

Leu Arg Thr Val Arg Asn Asn Phe Ala Ala Leu Thr Asn Leu Gln Asp
100 105 110

Arg Ala Pro Ser Lys Arg Ser Pro Met Cys Asn Gln Pro Ser Ile Asn
115 120 125

Lys Ala Thr Ile Thr Glu Glu Ala Tyr Gln Lys Leu Ala Ser Glu Thr
130 135 140

Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Leu Gln Thr
145 150 155 160

Arg His Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu
165 170 175

Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln
180 185 190

Val Ser Glu Phe Ile Ser Asn Thr Phe Leu Asp Lys Gln His Glu Val
195 200 205

Glu Ile Pro Ser Pro Thr Gln Lys Glu Lys Glu Lys Lys Lys Arg Pro
210 215 220

Met Ser Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
225 230 235 240

Thr Asn Ser Ser Ile Pro Arg Phe Gly Val Lys Thr Glu Gln Glu Asp
245 250 255

Val Leu Ala Lys Glu Leu Glu Asp Val Asn Lys Trp Gly Leu His Val
260 265 270

Phe Arg Ile Ala Glu Leu Ser Gly Asn Arg Pro Leu Thr Val Ile Met
275 280 285

His Thr Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Pro
290 295 300

Val Asp Thr Leu Ile Thr Tyr Leu Met Thr Leu Glu Asp His Tyr His
305 310 315 320

Ala Asp Val Ala Tyr His Asn Asn Ile His Ala Ala Asp Val Val Gln
325 330 335

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Glu Ala Val Phe Thr
340 345 350

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ser Ala Ile His Asp Val
355 360 365

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
370 375 380

Leu Ala Leu Met Tyr Asn Asp Ser Ser Val Leu Glu Asn His His Leu
385 390 395 400

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu Asn Cys Asp Ile Phe Gln
405 410 415

Asn Leu Thr Lys Lys Gln Arg Gln Ser Leu Arg Lys Met Val Ile Asp
420 425 430

Ile Val Leu Ala Thr Asp Met Ser Lys His Met Asn Leu Leu Ala Asp
435 440 445

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
    450   455   460

Leu Leu Asp Asn Tyr Ser Asp Arg Ile Gln Val Leu Gln Asn Met Val
465   470   475   480

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Pro Leu Gln Leu Tyr Arg
                485   490   495

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Arg Gln Gly Asp Arg
            500   505   510

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Asn
        515   520   525

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
    530   535   540

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val His Pro Asp Ala Gln Asp
545   550   555   560

Ile Leu Asp Thr Leu Glu Asp Asn Arg Glu Trp Tyr Gln Ser Thr Ile
                565   570   575

Pro Gln Ser Pro Ser Pro Ala Pro Asp Asp Pro Glu Glu Gly Arg Gln
            580   585   590

Gly Gln Thr Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Asp Gly
        595   600   605

Glu Ser Asp Thr Glu Lys Asp Ser Gly Ser Gln Val Glu Glu Asp Thr
    610   615   620

Ser Cys Ser Asp Ser Lys Thr Leu Cys Thr Gln Asp Ser Glu Ser Thr
625   630   635   640

Glu Ile Pro Leu Asp Glu Gln Val Glu Glu Glu Ala Val Gly Glu Glu
                645   650   655

Glu Glu Ser Gln Pro Glu Ala Cys Val Ile Asp Asp Arg Ser Pro Asp
            660   665   670

Thr Thr Gly Ile Leu Gln Ser Thr Val Pro Arg Ala Arg Asp Pro Pro
        675   680   685

Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val
    690   695   700

Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser
705   710   715   720

Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu
                725   730   735

Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu
            740   745   750

Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp
        755   760   765

His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr
    770   775   780

Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr
785   790   795   800

Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu
                805   810   815

Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys
            820   825   830

Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys
        835   840   845

Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu
    850   855   860

Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile
865   870   875   880

Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln
            885   890   895
Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu
        900   905   910
Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu
    915   920   925
Tyr Lys
930

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

GTAAGCTTCG AACATGATGC ACGTGAATAA TTTTCCC 37

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

GTAAGCTTCG AACATGGAGG CAGAGGGCAG CAGC 34

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

GTAAGCTTCG AACATGGCTC AGCAGACAAG CCCG 34

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

GTGAATTCCC GTCGTGTCAG GAGAAGCATC ATCTATG 37

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

GTGAATTCAA CCATGGAGCG GGCC 24

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

GTGGTACCCA GTTCCGCTTG GCC 23

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

GTCTCGAGGC AAGATGGCTG ACCC 24

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

GTGGATCCGA GCTCTTGACT TCGGG 25

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

GTAAGCTTAC ATGAGCTGGT CACCTTCCCT G 31

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

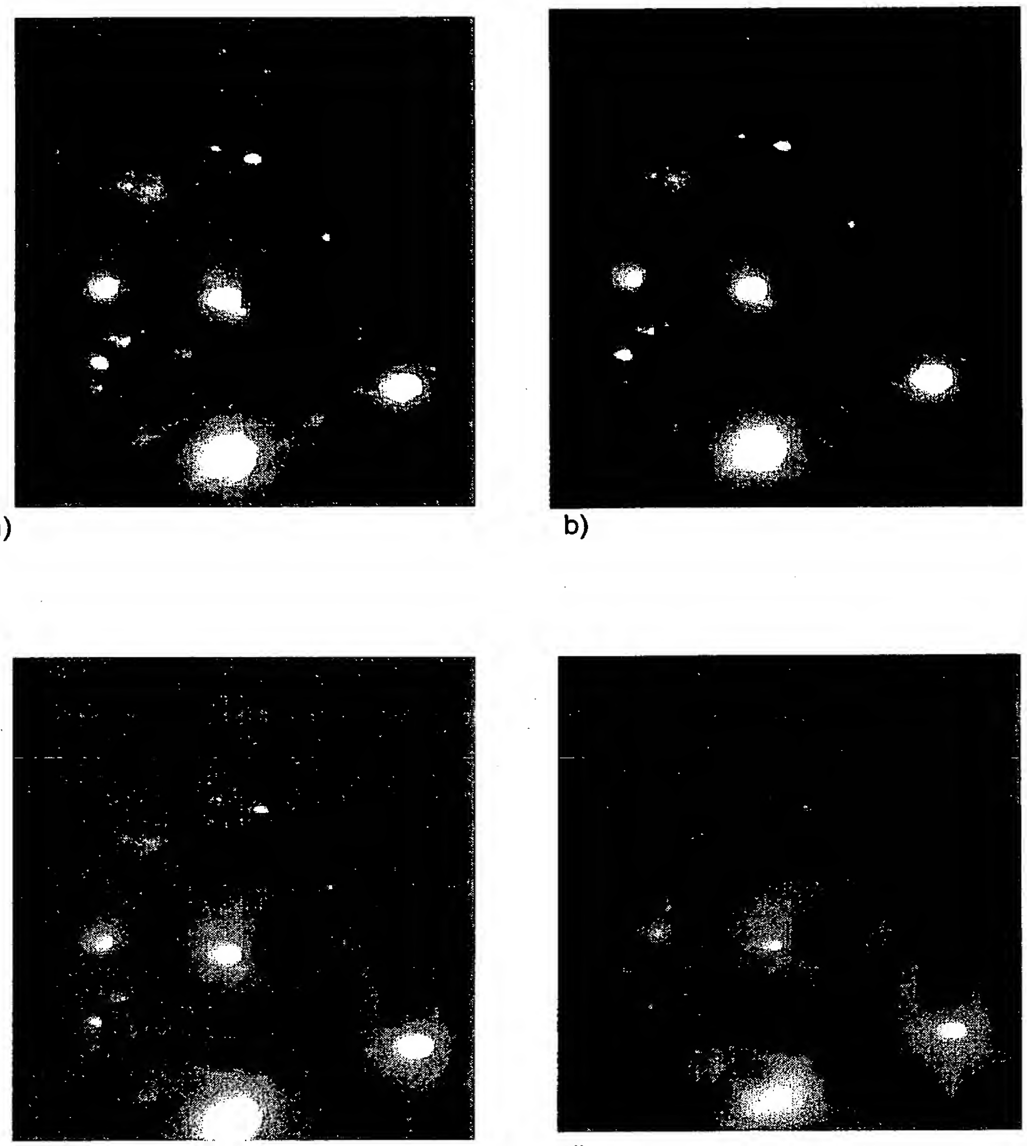
(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

GTGGTACCCA TGAGGCCTGC TCCAG 25

22/2 7DKL

Figure 1



a) b) c) d)

22129DK1

Figure 2

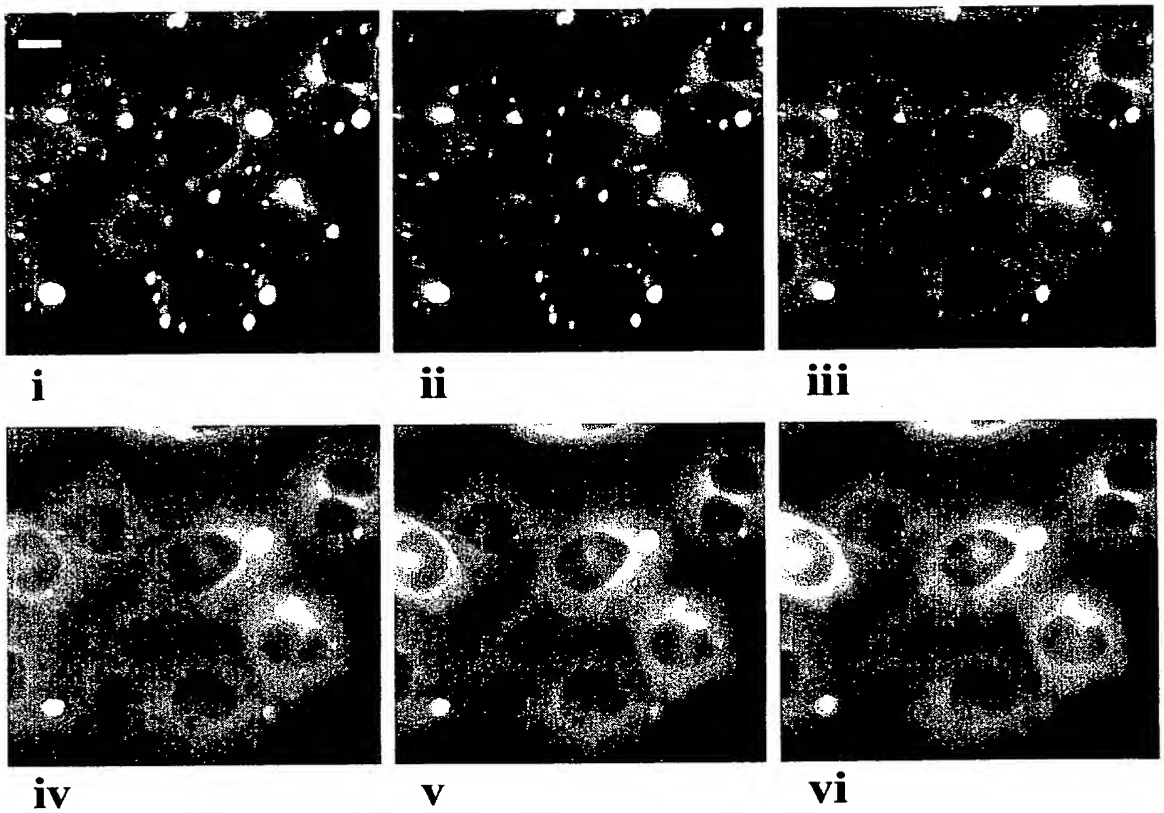


Figure 3

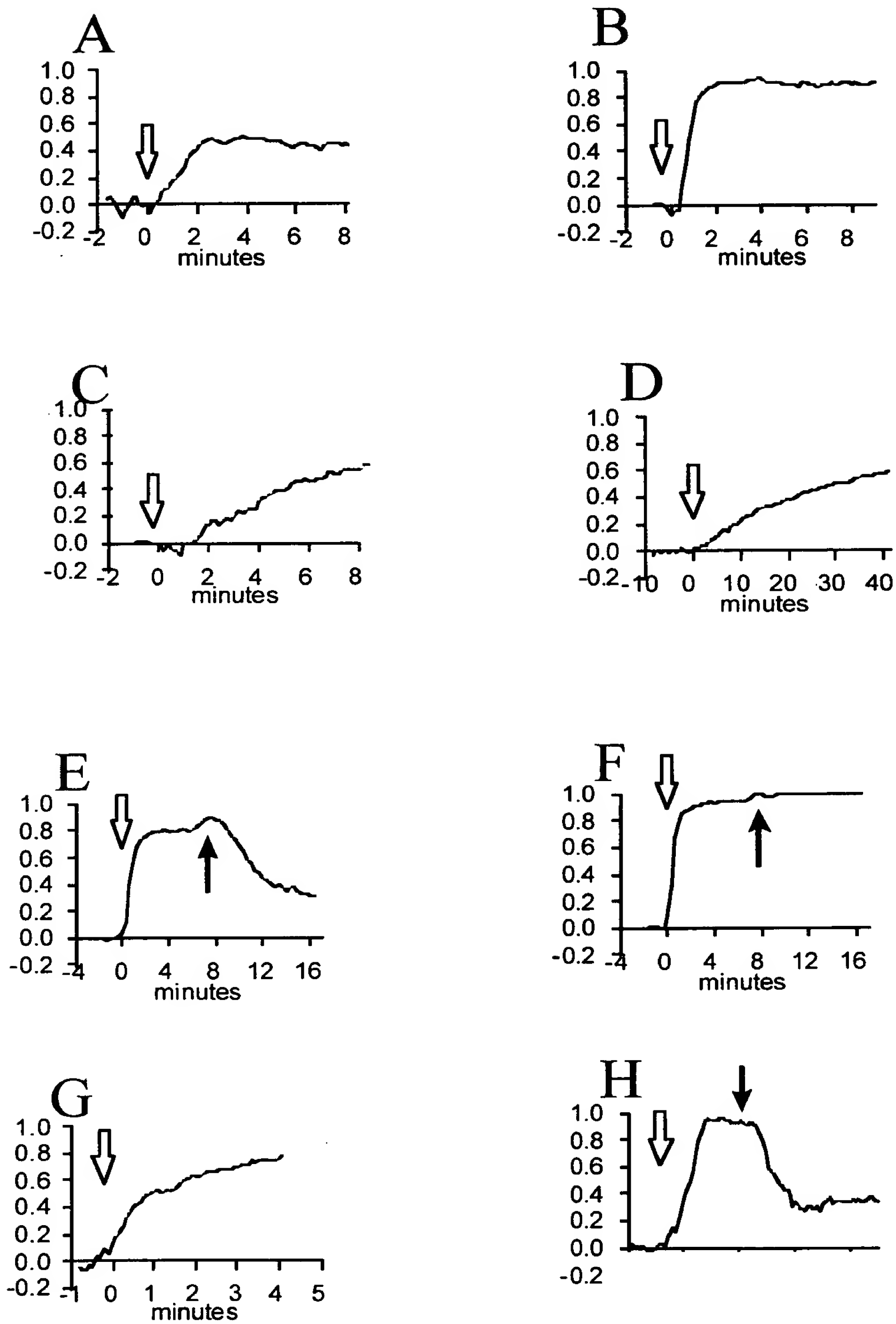

A
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-2 0 2 4 6 8
minutes
B
-2 0 2 4 6 8
minutes
C
-2 0 2 4 6 8
minutes
D
-10 0 10 20 30 40
minutes
E
-4 0 4 8 12 16
minutes
F
-4 0 4 8 12 16
minutes
G
-1 0 1 2 3 4 5
minutes
H

Figure 4

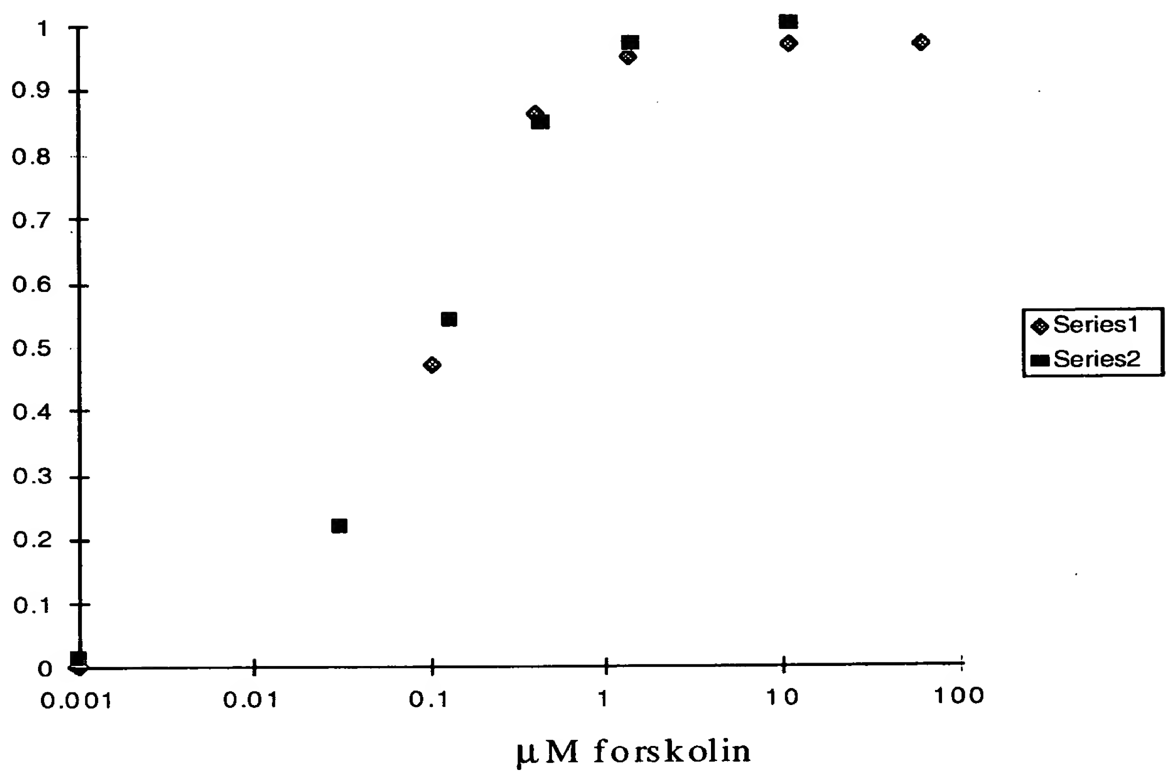

1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.001
0.01
0.1
1
10
100
μM forskolin
Series1
Series2

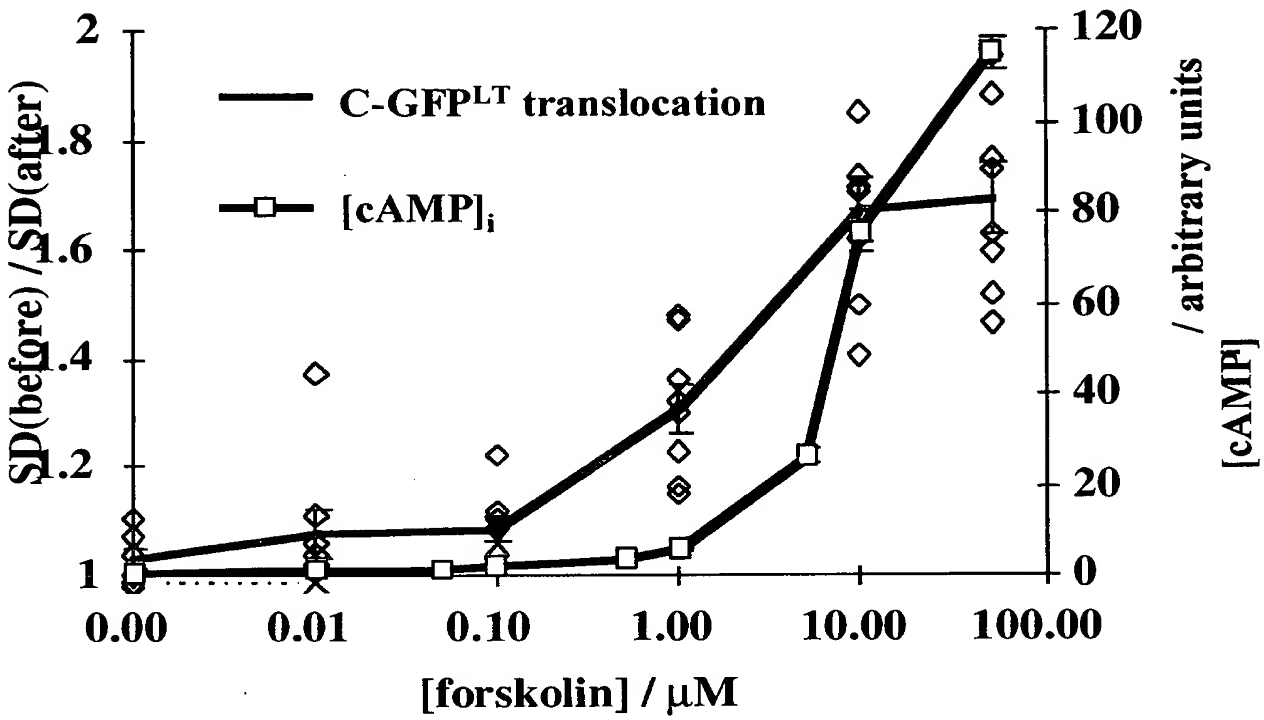
Figure 5

[forskolin]μM	$t_{1/2max}$/ s	t_{max} / s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

L21290K1

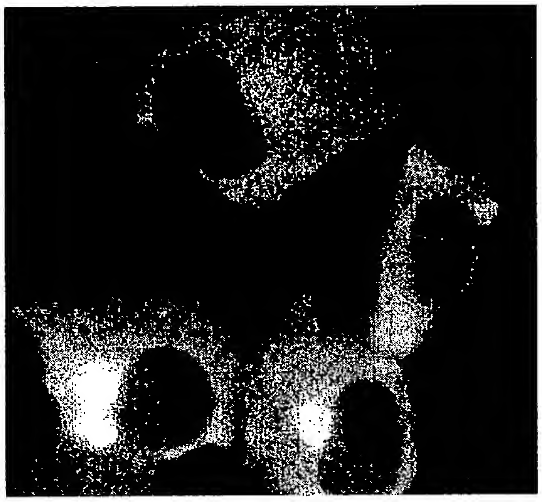
Modtaget PD
15 OKT. 1998

Figure 6



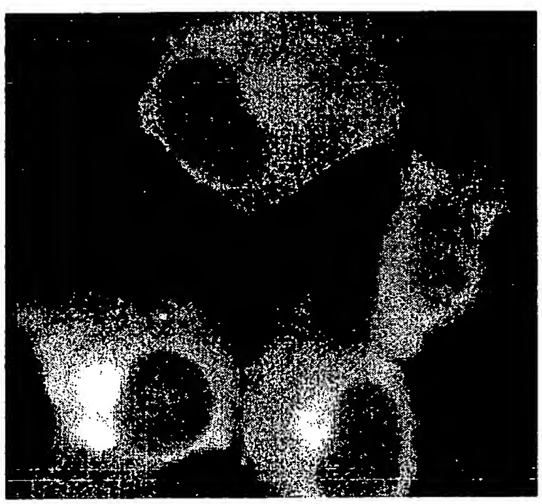
22129DK1

Figure 7



a)

b)



c)

ᒧᒧ/ᒪ7 UK/

Figure 8

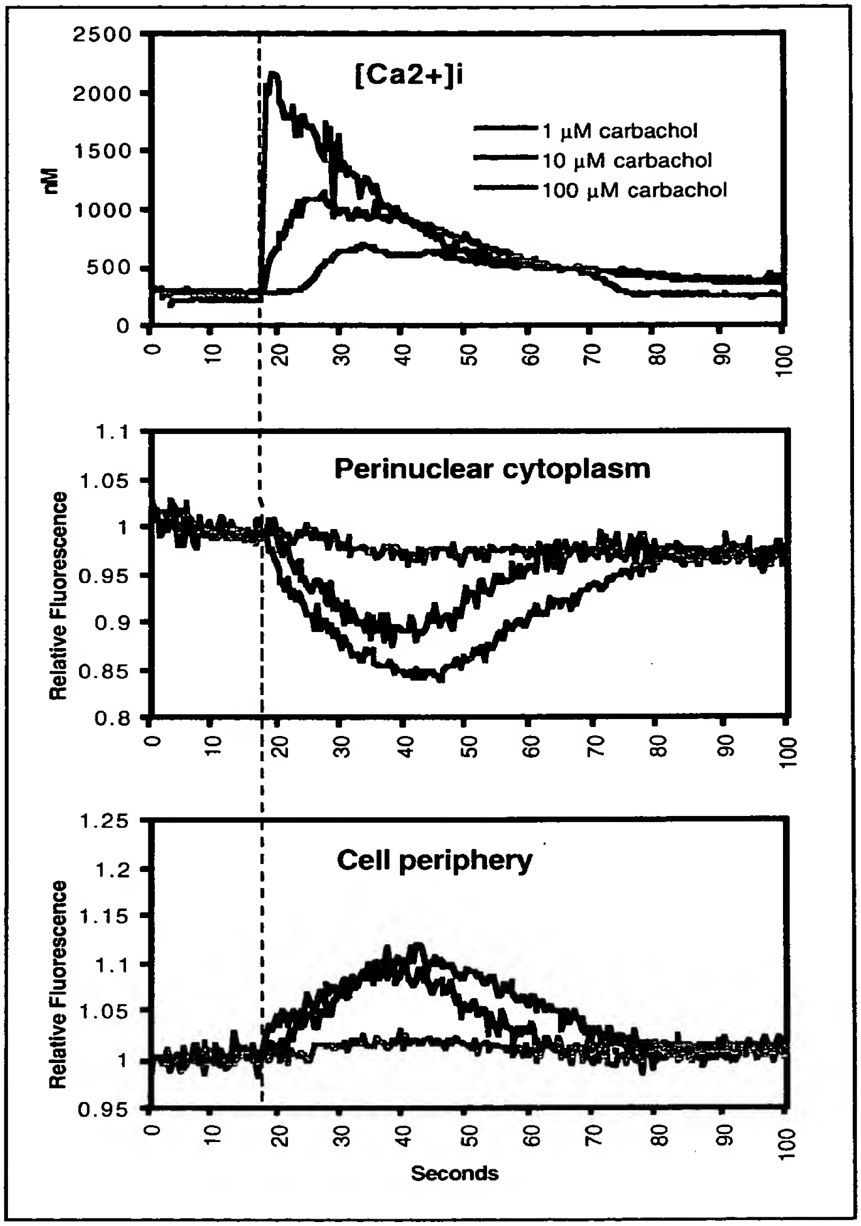
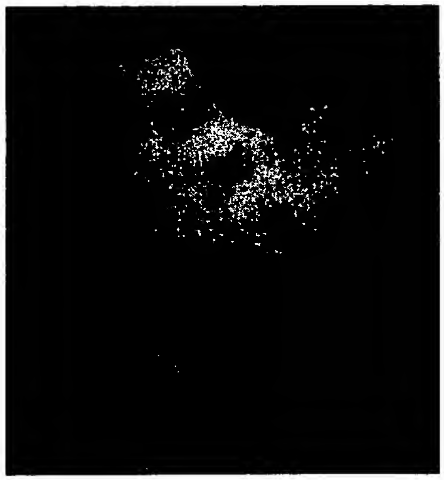
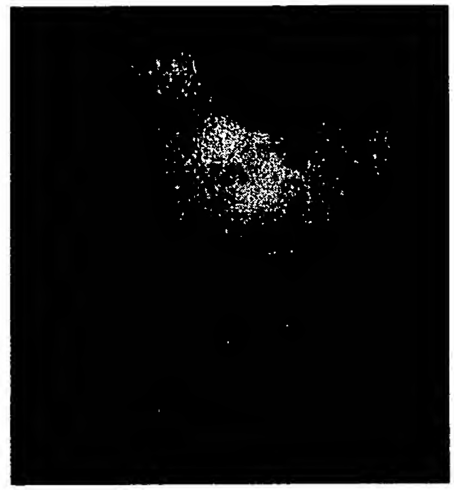


Figure 9

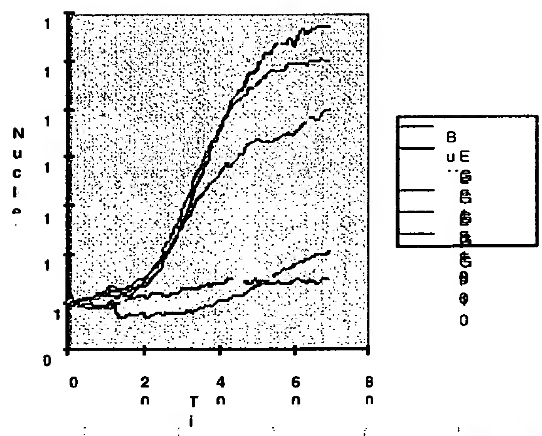


a)



b)

c)



d)

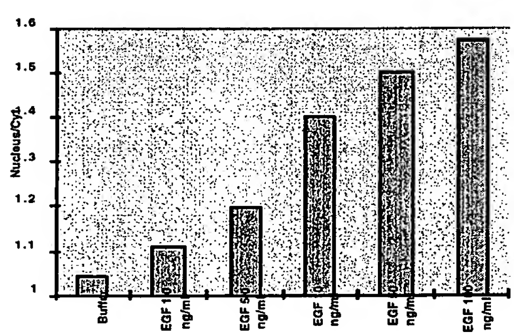
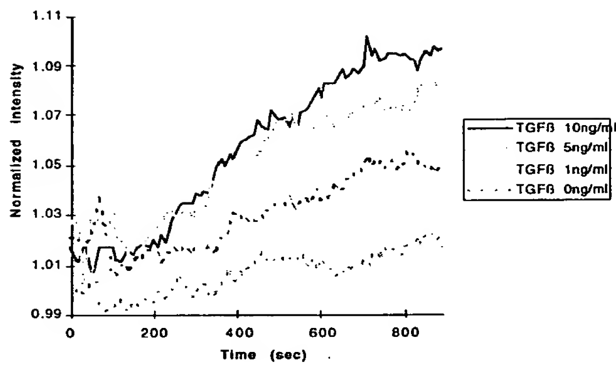


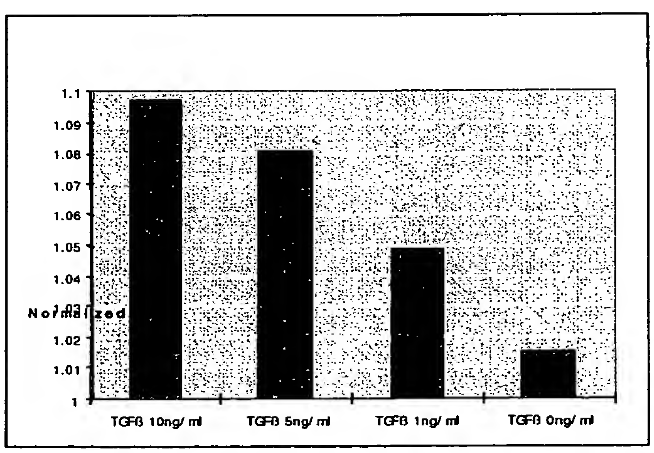
Figure 10

a)

b)



c)



2 2 (2 9 DK 1

Modtaget PD
15 OKT. 1998

Figure 11

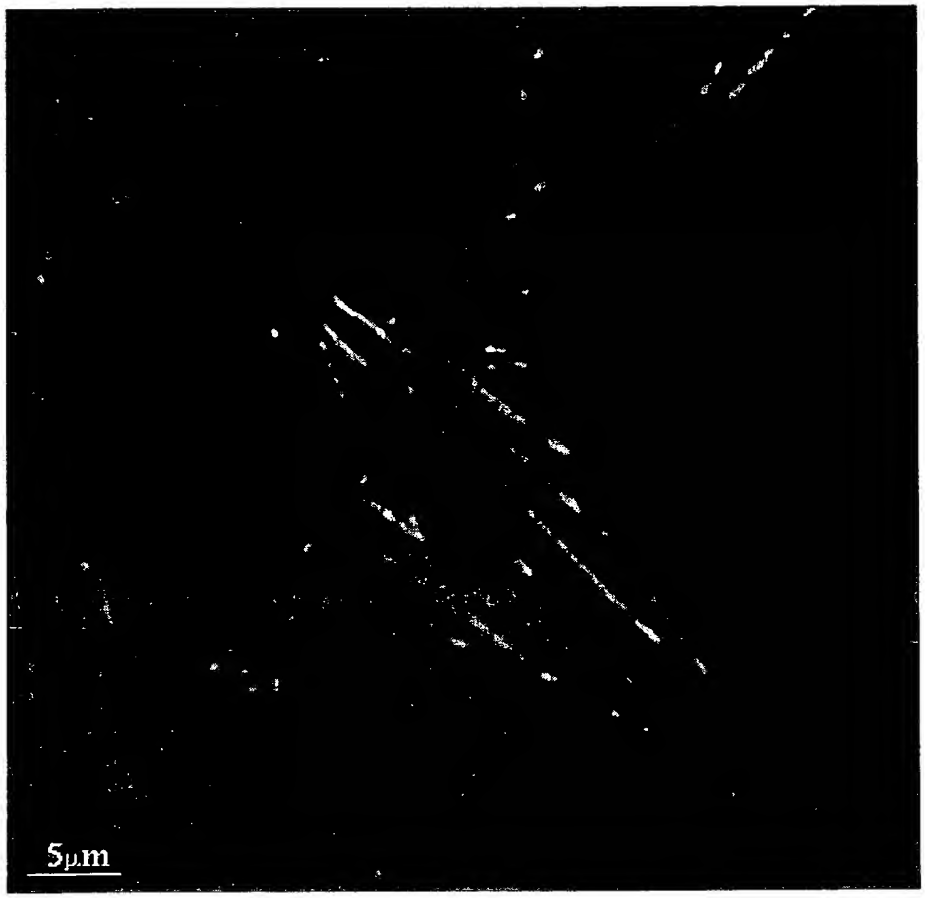


Fig. 12

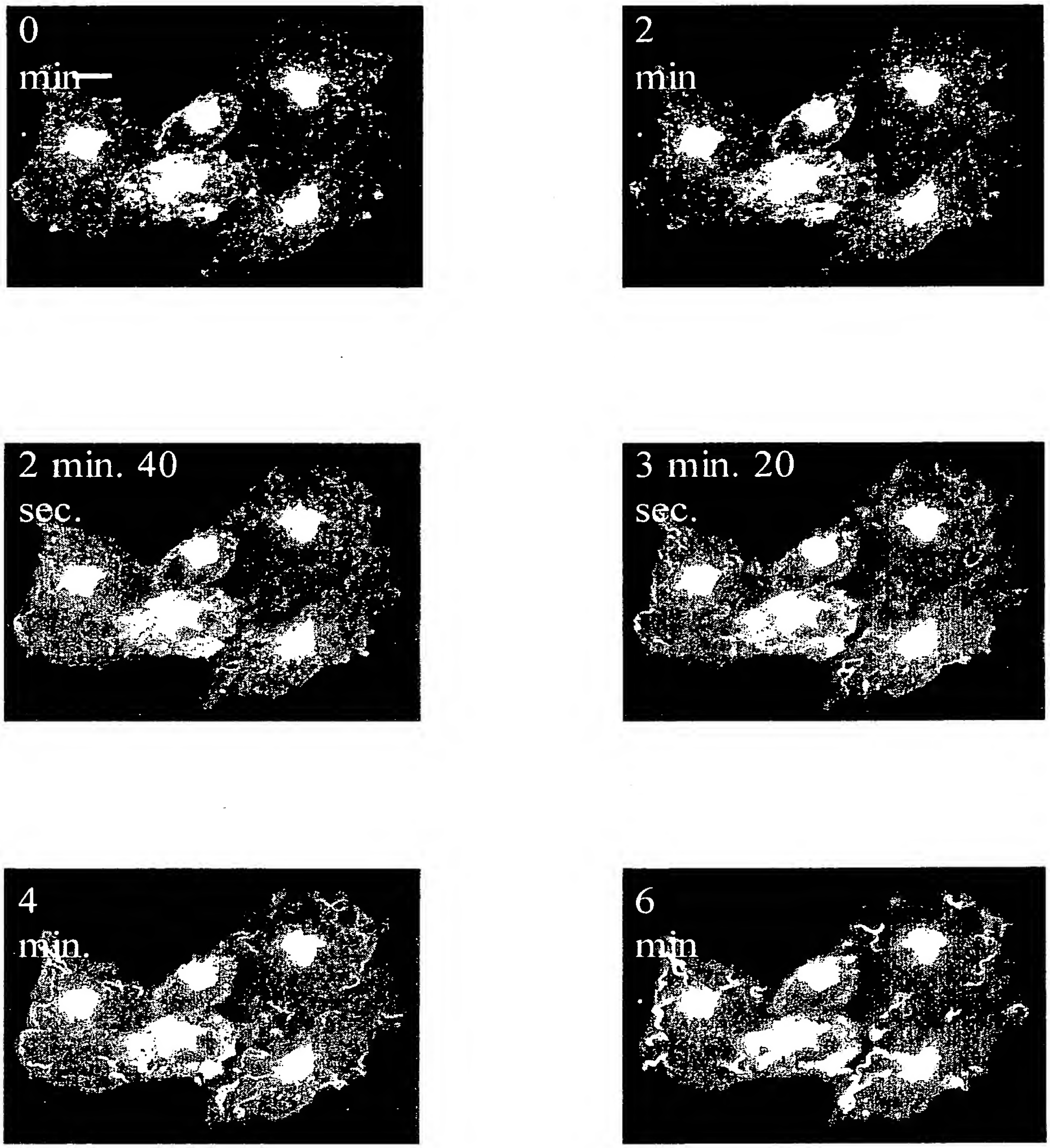


Figure 13

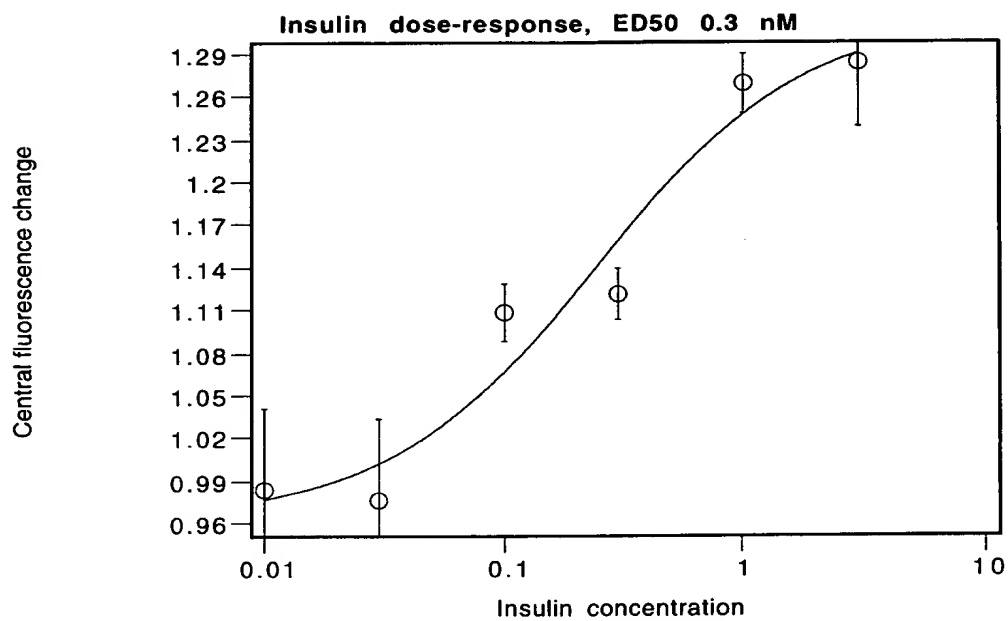

Insulin dose-response, ED50 0.3 nM
Central fluorescence change
1.29
1.26
1.23
1.2
1.17
1.14
1.11
1.08
1.05
1.02
0.99
0.96
0.01
0.1
1
10
Insulin concentration

Figure 14

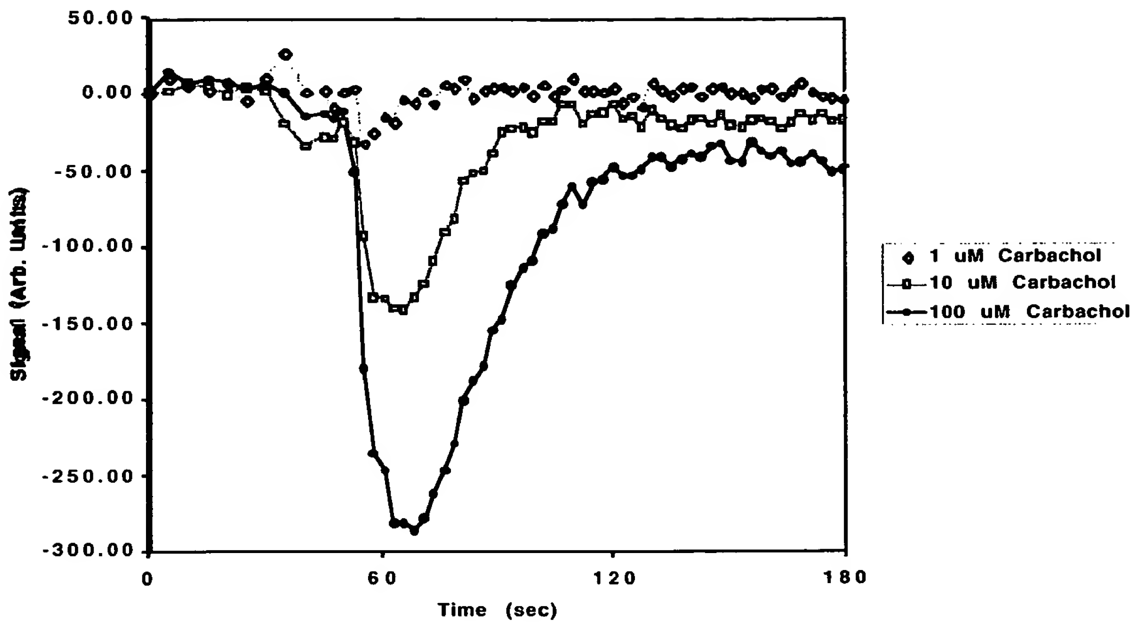
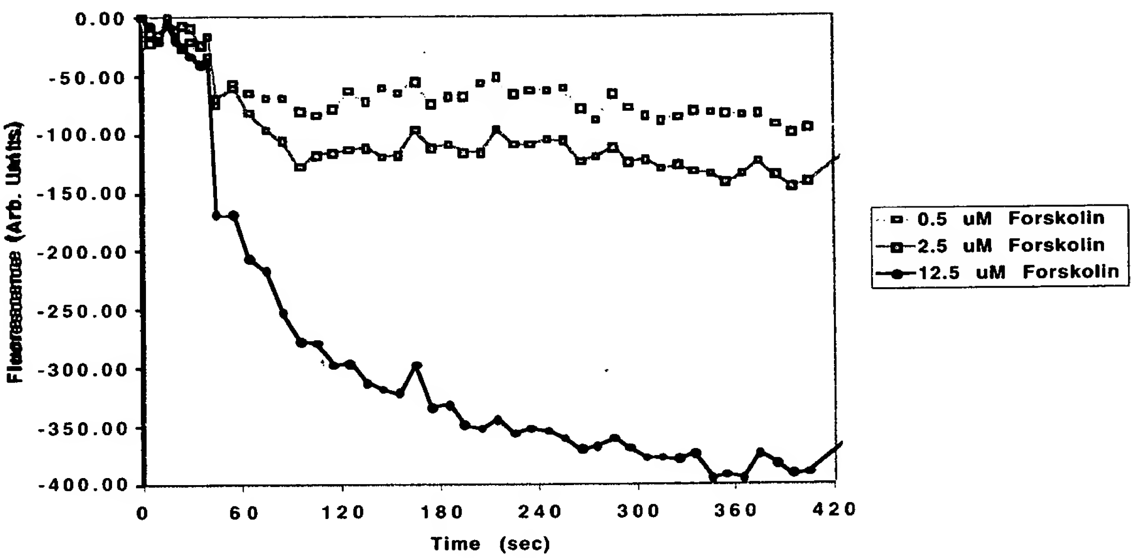
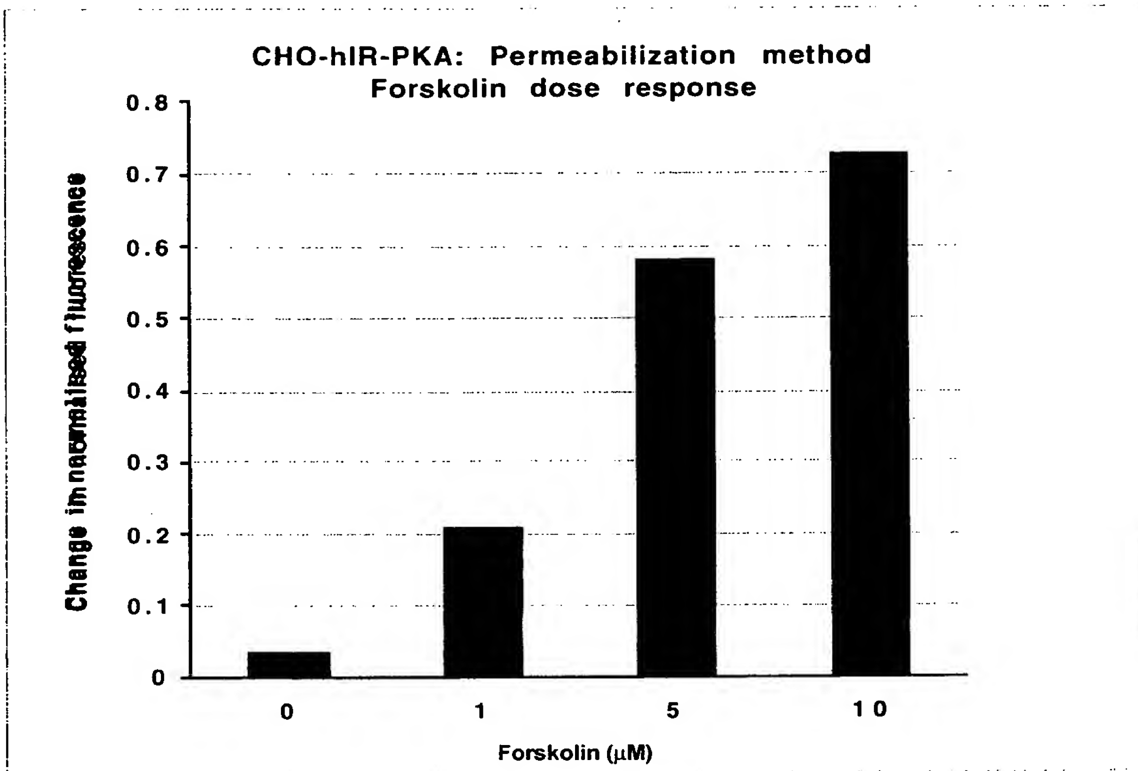

50.00
0.00
-50.00
-100.00
-150.00
-200.00
-250.00
-300.00
Signal (Arb. Units)
0
60
120
180
Time (sec)
1 uM Carbachol
10 uM Carbachol
100 uM Carbachol

Figure 15


0.00
-50.00
-100.00
-150.00
-200.00
-250.00
-300.00
-350.00
-400.00
Fluorescence (Arb. Units)
0
60
120
180
240
300
360
420
Time (sec)
0.5 uM Forskolin
2.5 uM Forskolin
12.5 uM Forskolin

L2129DK1

Figure 16



Changes in intracellular cAMP visualised using a cAMP-dependent protein kinase-green fluorescent protein hybrid.

Kasper Almholt, Bernard R. Terry*, Ole Skyggebjerg, Søren Tullin, Kurt Scudder, and Ole Thastrup

BioImage, Novo Nordisk A/S, 28 Mørkhøj Bygade, DK-2860 Søborg.

Keywords: PKA, cAK, C-subunit, cAMP, measurement, live-cell, GFP, redistribution

*corresponding author: Tel.: +45 4442 6341
Fax: +45 4442 1411
e-mail: bobt@novo.dk

22129DK1 Appendix I

ABSTRACT

A novel method to monitor changes in intracellular cAMP concentration ($[cAMP]_i$) within intact living cells has been developed based on a fusion of the catalytic subunit of cAMP-dependent protein kinase to green fluorescent protein (GFP). In stably transfected unstimulated fibroblasts, fusion protein fluorescence was highly concentrated in aggregates throughout the cytoplasm and absent in the nucleus. Stimulation with the adenylate cyclase activator forskolin caused the release of tagged catalytic subunits from the cytoplasmic aggregates within minutes, resulting in an increasingly homogeneous distribution of GFP fluorescence throughout the cytoplasm. The observed redistribution was completely reversible: removal of forskolin led to the return of fluorescence to the cytoplasmic aggregates. Spot-photobleach measurements showed that the rate of exchange of GFP-labelled catalytic subunits at these aggregates increased in proportion to $[cAMP]_i$. The localisation of the fusion protein was also sensitive to receptor stimulation. In fibroblasts stably expressing the G_s-protein coupled glucagon receptor, generation of an increased $[cAMP]_i$ through glucagon stimulation resulted in a redistribution of tagged catalytic subunit similar to that observed after forskolin addition. Conversely, in fibroblasts overexpressing the G_i-protein coupled α2a adrenoreceptor, addition of norepinephrine after forskolin stimulation led to a reversal of the fusion protein redistribution.

INTRODUCTION

The cAMP-dependent protein kinase (cAK)[1] is a ubiquitous serine/threonine protein kinase. cAK is recognised as the only mediator of intracellular cAMP signals in eukaryotes[2], with the exception of certain ion channels[3]. The cAK holoenzyme is an R_2C_2 tetramer consisting of a regulatory (R) dimer and two catalytic (C) subunits[2]. Presently, four isoforms of the regulatory subunit (RIα, RIβ, RIIα and RIIβ) and three isoforms of the catalytic subunit (Cα, Cβ and Cγ) have been described[2]. Splice variants of Cα and Cβ[4] and possible R heterodimers, as reported for RIα and RIβ[5], add to the complexity of the cAK holoenzyme. Although the Cγ isoform is unique with respect to substrate specificity, inhibition and tissue distribution[6], few reports suggest different roles for Cα and Cβ isoforms of the catalytic subunit[7]. In contrast, the RI and RII subunits are reported to be distinct. The cAKI (RI_2C_2) holoenzyme is thought to be mainly soluble and cytoplasmic[2] although RI is reported to be associated with

sarcoplasmic membranes[8] and also with a detergent-resistant structure in mammalian sperm[9]. cAKII (RII_2C_2) on the other hand is thought to be particulate and RII has been reported to bind to a number of intracellular components, most notably Golgi membranes[10,11] and centrosomes[10,11] but also mitochondria[12], nuclei[13,14] and cytoskeletal components[11,12]. RII subunits interact with a family of proteins called A-kinase anchoring proteins (AKAP)[15] and this may also be true of RI subunits[16]. The AKAP-RII subunit interaction is presumed to be responsible for localising the cAKII tetramer at these intracellular sites. The NH_2-terminus of the C subunit is myristoylated[17], a post-translational modification usually associated with membrane insertion. However, the C subunit does not appear to be membrane attached and while myristoylation may increase the thermostability of the protein, the possible role of myristoylation in its targeting or substrate specificity is still not clear[18].

The C subunit in the assembled tetramer is believed, although not unanimously[19], to be catalytically inactive. Activation of cAK is physiologically mediated through G_s-protein coupled plasma membrane receptors. G_s-protein activation leads to activation of adenylate cyclases, which generate cAMP. Binding of two molecules of cAMP to each R subunit causes the release and activation of the C subunits. Dissociated C subunits phosphorylate cytoplasmic substrates[20,21] and have been shown to relocalise to the nucleus[22]. The nuclear redistribution mechanism of C subunits may be by simple diffusion through nuclear pores[21]. To date a large number of cytoplasmic and a few nuclear cAK substrates have been reported. An incomplete list of 25 *in vitro* substrates[23] includes several enzymes involved in basic metabolism such as phosphorylase kinase, glycogen synthase and fructose bisphosphatase. Nuclear C subunit regulates transcription of genes under control of the cAMP response element (CRE) by phosphorylating the continuously bound CRE binding protein, (CREB)[24,25].

Several factors decrease the level of cAK activity. Stimulation of plasma membrane bound G_i-protein coupled receptors inhibits adenylate cyclases and cAMP is continuously being broken down by a variety of phosphodiesterases. Despite the importance of the cAMP/cAK signalling pathway, there is no easy method to monitor intracellular cAMP concentrations ($[cAMP]_i$) in intact living cells. The current method of choice involves fluorescence resonance energy transfer (FRET) between microinjected fluorescently labelled R and C subunits[26]. In the work described herein, the Cα subunit was tagged with a highly fluorescent variant of green fluorescent protein (GFP) containing F64L and S65T amino acid substitutions (GFP^{LT}) (International

Publication No. WO97/11094). This approach provides a transfectable probe for monitoring the intracellular trafficking of C subunits in response to changes in $[cAMP]_i$ and represents the first easy method to evaluate changes in $[cAMP]_i$ in intact living cells in response to extracellular signals.

Results

GFP^{LT} tagged C had the expected molecular weight.

Lysates of glucagon receptor-transfected baby hamster kidney cells (BHK/GR) stably expressing the C-GFP^{LT} fusion protein were characterised by Western blot analysis using polyclonal antibodies directed against the NH_2-terminus of Cα (Fig. 1). In a separate experiment, lysates of BHK cells, transiently expressing either of the two fusion proteins, were characterised by Western blot analysis using polyclonal antibodies that recognise GFP (data not shown). Taken together, these experiments show that C-GFP^{LT} fusion protein is recognised as a unique protein of the expected size by the anti-Cα antibody in stably transfected cells and that both fusion proteins have the same molecular weight.

The fusion protein localised to cytoplasmic aggregates.

The localisation of the two fusion proteins, when transiently expressed in Chinese hamster ovary (CHO) cells, was very different. While GFP^{LT}-C was evenly distributed throughout the cytoplasm (Fig. 2A), C-GFP^{LT} was found in highly fluorescent aggregates in the cytoplasm (Fig. 2B). These distinct patterns for the two fusions was also seen in transiently transfected human embryonic kidney (HEK293) and BHK/GR cells (data not shown). For unknown reasons it was not possible to make stable transfectants expressing the GFP^{LT}-C fusion, whereas this procedure was straightforward with the C-GFP^{LT} fusion. The distribution of GFP^{LT}-C in transiently transfected CHO cells did not change when $[cAMP]_i$ was raised by the addition of 50 μM forskolin (n=6, data not shown). The following results are therefore based only on work with the C-GFP^{LT} fusion.

Increased [cAMP]$_i$ caused the release of fusion protein from cytoplasmic aggregates.

Within 2-3 minutes of treatment of CHO/C-GFP^{LT} cells with forskolin, C-GFP^{LT} fluorescence dispersed from the bright aggregates and filled the cytoplasm (Fig. 3A, 1 μM forskolin), remaining in this distribution for as long as forskolin was present (cells were followed up to two hours). The probe did not enter the nuclear compartment to any clearly observable extent. Higher doses of forskolin increased the rate and extent of probe redistribution. The responses depicted in Figure 3B-G have all been quantified from image data, as described in the experimental protocol. Table 1 gives a comparison of the average temporal profiles of fusion protein redistribution in response to the three forskolin concentrations shown in Figure 3B. Addition of 1 mM dibutyryl cAMP (dbcAMP) (n=6), a membrane permeable cAMP analogue, which is not degraded by phosphodiesterases, caused a similar but slower response (Fig. 3C). Addition of 100 μM 3-isobutyl-1-methylxanthine (IBMX) (n=4), a cell permeable phosphodiesterase inhibitor, caused a similar, slow response (Fig. 3D), even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown). As a control for the behaviour of the fusion protein, GFP^{LT} alone was expressed in CHO cells and these also given 50 μM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

To test the reversibility of the fusion protein redistribution, CHO/C-GFP^{LT} cells were treated with 10 μM forskolin (n=2) and washed repeatedly (5-8 times) with 37°C buffer. Although the plant terpenoid forskolin is lipophilic, it is possible to remove its effect by washing with aqueous buffer[22]. In these experiments, fusion protein began to return to its prestimulatory localisation within 2-3 min (Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation. To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP]$_i$, cells were treated with a combination of 10 μM forskolin and 100 μM IBMX (n=2); when washed repeatedly (5-8 times) with 37°C buffer containing 100 μM IBMX the fusion protein did not return to its prestimulatory localisation after removal of forskolin (Fig. 3E).

To test the probe's response to receptor activation of adenylate cyclase, stably transfected BHK/GR,C-GFP^{LT} cells were exposed to glucagon stimulation. In these cells, addition of 100 nM glucagon (n=2) caused the release of C-GFP^{LT} from the cytoplasmic aggregates and a resulting permanent redistribution of the fusion protein to

a more even cytoplasmic distribution within 2-3 min (Fig. 3F). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown). CHO/C-GFP^{LT} cells, transiently transfected with the α2a adrenoreceptor (ARα2a), were treated with 10 μM forskolin then, in the continued presence of forskolin, exposed to 10 μM norepinephrine to stimulate the exogenous adrenoreceptors. This treatment led to reaggregation of C-GFP^{LT} within the fluorescent structures, consistent with a receptor-induced decrease in $[cAMP]_i$ (Fig. 3G).

Rate of recovery from photobleach of C-GFP^{LT} aggregates is dependent on forskolin concentration.

Photobleach measurements were made to confirm that changes seen in the distribution of C-GFP^{LT} fluorescence were a result of changes in the rate of turnover of C-GFP^{LT} upon the aggregates. The fluorescence of an entire C-GFP^{LT} aggregate within a cell could be effectively bleached within 2 to 5 seconds by a stationary laser beam at full intensity. After bleaching, aggregates recovered their fluorescence, indicating a dynamic exchange of C-GFP^{LT} at these loci (Fig. 4A). The rate of recovery from spot photobleach was highly reproducible at each particular concentration of forskolin even in different cells (Fig. 4B). Both the extent and rate of recovery increased with the forskolin treatment given. Most recovery curves required at least two exponentials to fit them adequately. Given the limits of the experimental procedure, the curves are used here only to estimate half-times of recovery. To an approximation, half times for recovery can be estimated directly from the slope of reciprocal plots of the fluorescence displacement for the first few time points[27]. Values for half times estimated within the first 3.0 seconds of recovery (Fig. 4C) are plotted as a dose response curve in Figure 5, giving an estimated ½-maximal concentration for forskolin of about 3 μM

Fusion protein redistribution correlated with $[cAMP]_i$

As described above, the time it took for a response to come to completion was inversely related to the forskolin dose (Table 1). In addition the extent of a response was also dose dependent. In an automated imaging system we stimulated CHO/C-GFP^{LT} cells with 5 increasing doses of forskolin (n=8). Images were analysed with the same algorithm used

to construct Figure 3B-G. From the results shown in Figure 5, a half maximal stimulation was observed at 1.7 μM forskolin by this method. In parallel, CHO/C-GFP^{LT} cells were stimulated with 8 increasing concentrations of forskolin (n=N) and the relative amount of cAMP produced was measured in a scintillation proximity assay (SPA). The ½-maximal concentration for forskolin in the SPA assay was determined to be 9.3 μM (Fig. 5).

Co-localisation of C-GFP^{LT} with labelled ceramide distributions

Figure 6A is an overlay of green and red fluorescence emissions from CHO/C-GFP^{LT} cells stained with BODIPY® FL C_5-ceramide (ceramide-FL). The green channel contains the ceramide-FL and GFP^{LT} fluorescence; the red channel shows only the ceramide-FL excimer emission. The ceramide-FL probe preferentially accumulates in Golgi membranes[28]. This is most obvious in images formed from the red excimer emissions of the FL-ceramide. The GFP^{LT}-bright structures do not stain with the ceramide probe indicating that they are clearly distinct from Golgi membranes.

Structure of the GFP^{LT} -bright aggregates

Figure 6B shows an iso-surface rendering of 25 deconvolved and reconstructed through-focus wide-field images of a single large C-GFP^{LT} aggregate. Each aggregate appears to have the structure of a convoluted tubule or glomerulus, and this is more obvious in the stereo pair (Fig. 6C) derived from the same data set from which the iso-surface rendering was made. It is not completely clear whether each structure is formed from a single fully connected tubule or a small number of discrete tubules in close apposition. The structure is however clearly compact and more complex and structured than a simple amorphous aggregation of C-GFP^{LT} molecules. Figure 6B-C is typical of the larger aggregates which are of the order of 2 to 4 μm across. The more numerous smaller aggregates (less than 1 μm across) appear to share the same underlying structural component(s) as their larger counterparts.

Discussion

The aim of the present study was to develop a transfectable probe for monitoring changes in $[cAMP]_i$. Since cAK is by far the major intracellular effector for cAMP[2], a measure of its activation should closely reflect physiologically relevant changes in $[cAMP]_i$.

NH_2- and COOH-terminal fusions of C subunit were made to a highly fluorescent variant of GFP. Only the C-GFP^{LT} fusion responded to changes in $[cAMP]_i$. The three-dimensional structure of the C subunit[29,30] reveals that both the NH_2- and COOH-termini, while far apart, are both located opposite the catalytic cleft and close to the surface of the protein. Comparison with the closely related cGMP-dependent protein kinase, whose R and C subdomains are contained within the same polypeptide chain in R-C order[31], suggests that the R subunit of cAK may be expected to interact with the NH_2-terminal region of the C subunit. Furthermore, the surface of the C subunit in the NH_2-terminal region is hydrophobic[29], supportive of a protein-protein interaction in this area. An NH_2-terminal GFP^{LT} tag would also prevent post-translational myristoylation (of the NH_2-terminus) of the C subunit as reported specifically for mouse $C\alpha$[18], while the C-GFP^{LT} fusion may well be myristoylated. These factors may explain the very different behaviours of the NH_2- and COOH-terminal fusions of C subunit to GFP^{LT}.

There are reasons to believe, that the C-GFP^{LT} fusion protein behaves like the endogenous kinase both with regard to localisation and activation kinetics. Li *et al.* (1996)[11] have, for instance, reported that RII subunits occur as "intensely fluorescent spots" within perinuclear cytoplasm. Skålhegg *et al.* (1997)[32] also reported a granular distribution of RII in both human B and T lymphocytes. Also, the time frame of fusion protein redistribution in response to forskolin addition reported here, corresponds well to the observation of dissociation of microinjected $RI\alpha_2C\alpha_2$ holoenzyme in response to forskolin within 1-2 minutes[26] and the dissociation of endogenous RII_2C_2 in response to forskolin observed by immunofluorescence after less than 5 min[22].

In contrast with previous work with microinjected $RII\alpha_2C\alpha_2$ holoenzyme and $C\alpha$ subunit[21], we did not observe any translocation of C-GFP^{LT} to the nucleus. A possible explanation could be the increased size of the fusion protein relative to endogenous C subunit. Nuclear pores are thought to allow passage by diffusion of globular proteins of less than 45-60 kDa[33]. The putative size limit of 45-60 kDa may adequately explain the exclusion of the fusion protein (68 kDa), yet passage of endogenous C subunit (41 kDa).

Consistent with this, a microinjected 65 kDa fusion protein of glutathione S-transferase and mouse Cα subunit (GST-C) was excluded from the nucleus[21].

That the C-GFP^{LT} fusion can be released by dbcAMP or treatments which increase $[cAMP]_i$ suggests that it must recognise and attach to endogenous R subunits (or some subset of the same) and therefore that these R subunits are naturally collected at or on the structures seen in Figures 3A and 6. Reversal of elevated $[cAMP]_i$, e.g. by removal of forskolin or stimulation of G_i-coupled receptors, results in rapid return of fluorescence to the original prestimulatory locations within cytoplasm. These anchoring structures therefore appear to be persistent features within the cytoplasm of CHO/C-GFP^{LT} cells. Similar structures and C-GFP^{LT} behaviour were also found in transfected BHK cells.

The distribution of fluorescence between aggregates and cytoplasm should reflect the position of a dynamic equilibrium within each cell, determined principally by $[cAMP]_i$. This is confirmed by results from spot-photobleach measurements. The rate of fluorescence recovery of aggregates following photobleach measures the net rate of turnover of C subunits at these sites. The rate of recovery is the sum of on and off rates for the association of catalytic with regulatory subunits at these loci, both of which will be governed principally by the concentration of cAMP within the cell (the off rate being governed directly by $[cAMP]_i$; the on rate being dependent on the concentration of free C-GFP^{LT} in the cytoplasm). Most aggregates completely disappear after full stimulation with forskolin. However, often one aggregate remains, and this is always the biggest and brightest from the unstimulated cell. Nevertheless, as photobleaching can demonstrate, there is active turnover of C-GFP^{LT} even at these large fluorescent aggregates which remain in fully stimulated cells. As a further observation, there appears to be considerable mobility of catalytic subunits within the structure of an aggregate, since a stationary laser beam (approx. 0.5-1.0 μm diameter) is able to bleach fluorescence from an entire aggregate of 2-3 μm diameter in 2 to 5 seconds.

The lack of colocalisation of C-GFP^{LT} and ceramide fluorescence, the position of aggregates within the cell and their unusual form, suggest that these structures are definitely not associated with Golgi, but may well be constructed of membrane tubules with C-GFP^{LT} on the outer surface. Although we have been unable as yet to ascertain the identity of these structures, we have ruled out Golgi membranes. They may however be membranous since fusion protein is apparently freely mobile on them, possible tubular judging by the 3-D recontructed image, and clearly the catalytic subunits are able to

bind to and release from R subunits with ease, suggesting that the latter are anchored to the surface of these structures. They are also persistent within the cytoplasm, and found in all cells transfected thus far with the C-GFP^{LT} construct (CHO, HEK293 and BHK).

Figure 5 gives a comparison of an SPA assay conducted in parallel with two different forskolin dose response experiments using the cAK fusion protein. These experiments showed a direct correlation of three parameters: level of $[cAMP]_i$, turnover rate of C-GFP^{LT} at cytoplasmic aggregates, and overall degree of fusion protein redistribution. Data from these three greatly varying methods agree on an ½-maximal concentration for forskolin of between 1.7 to 9.3 μM in this system. As these results show, the cAK fusion protein represents a novel and reliable probe by which dynamic changes in $[cAMP]_i$ can be measured in intact living cells as they respond to extracellular signals.

Experimental protocol

Hybrid cDNA construction

Hybrid cDNAs encoding NH_2- and COOH-terminal fusions of murine Cα subunit[34] to GFP^{LT} were inserted into the multiple cloning site of the pZeoSV (Invitrogen Corp., San Diego, CA, USA) mammalian expression vector, generating the fusion constructs C-GFP^{LT} and GFP^{LT}-C. Briefly, cDNAs encoding C and GFP^{LT} were amplified by PCR using the following primers: 5'-C, TTGGACACAAGCTTTGGACACCCTCAGGATATGGGCAACGCCGCCGCCGCC AAG; 3'-C, GTCATCTTCTCGAGTCTTTCAGGCGCGCCCAAACTCAGTAAACTCCTTGCCA CAC ; 5'-GFP^{LT}, TTGGACACAAGCTTTGGACACGGCGCGCCATGAGTAAAGGAGAAGAACTTT TC and 3'-GFP^{LT}, GTCATCTTCTCGAGTCTTACTCCTGAGGTTTGTATAGTTCATCCATGCCATGT . HindIII/AscI restriction endonuclease digested C subunit PCR amplification product and AscI/XhoI digested GFP^{LT} PCR product were ligated with the HindIII/XhoI digested vector for the generation of the C-GFP^{LT} fusion construct. Correspondingly the GFP^{LT}-C construct was generated by ligating HindIII/Bsu36I digested GFP^{LT} PCR product and Bsu36I/XhoI digested C subunit PCR product with the HindIII/XhoI digested vector. To

generate a similar construct which allowed the expression of GFP^{LT} alone, the GFP^{LT} PCR product was digested with HindIII/XhoI and ligated with the HindIII/XhoI digested vector.

Cell cultures

CHO cells were transfected with the vectors containing hybrid cDNA for the C-GFP^{LT} or the GFP^{LT}-C fusion proteins using the calcium phosphate precipitate method in HEPES-buffered saline[35]. Stable transfectants were selected using 1000 μg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 μg penicillin-streptomycin mixture ml^{-1}, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein redistribution, the constructs were stably expressed in BHK/GR cells (Novo Nordisk, Bagsværd, Denmark) overexpressing the human GR. Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 μg G418/ml (*Neo* marker) and C-GFP^{LT} was maintained with 500 μg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing cDNAs for C-GFP^{LT} and the human ARα2a (ATCC). Transfected cells are referred to as *e.g.* CHO/C-GFP^{LT} cells in the text.

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM's F12 medium with glutamax (Life Technologies), 100 μg penicillin-streptomycin mixture ml^{-1} and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Immunoblotting

Samples containing 10 μg of protein, determined according to the method of Bradford[36] using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Hercules, CA, USA), were added to SDS sample buffer[35] and run on precast 7.5 % SDS-PAGE gels with a 4 % stacking gel (Bio-Rad). The proteins were transferred to PH79 nitrocellulose membranes (Scleicher & Schuell GmbH., Dassel, Germany) for an hour at 4°C using a Bio-Rad Transfer Blot apparatus (80 V). Non-specific adhesion was blocked by

incubating the membranes over night in 3 % bovine serum albumin Fraction V (Sigma Chemical Company, St. Louis, MO, USA) in Tris-buffered saline (TBS) containing 50 mM Tris pH 7.5 and 0.15 M NaCl and for an hour in 3 % skim milk powder (Difco Laboratories, Detroit, MI, USA) in TBS with 0.1 % Tween20 (TBST). The membranes were incubated for an hour in TBST with 3 % skim milk powder and the primary polyclonal rabbit anti-Cα antibody (Upstate Biotechnology Inc., Lake Placid, NY, USA), which was raised against a peptide corresponding to a 16 amino acid N-terminal stretch of human Cα, diluted 1:1000. After 4 washes of 5 min each with TBST, secondary antibody (horse radish peroxidase-conjugated donkey anti-rabbit immunoglobulin from Amersham International plc, Buckinghamshire, UK) diluted 1:5000 in TBS with 3 % skim milk powder was added and incubated for an hour. After 4 washes in TBST and one in TBS, immunoreactivity was detected by enhanced chemiluminescence (ECL) as described by the manufacturer (Amersham) and exposed on Biomax® MR film (Eastman Kodak Company, Rochester, NY, USA). All the steps were performed at room temperature unless otherwise stated.

Time-lapse recording of fusion protein movement.

Cells were cultured in HAM's F12 medium as described above. The chambers were placed on a temperature regulated microscope stage and kept at 37°C. Fluorescence images were captured using an Axiovert 135 inverted light microscope (Carl Zeiss, Oberkochen, Germany) equipped with a Fluar x40, NA 1.3 oil immersion objective (Zeiss) and a cooled (-40°C) CH1 charged coupled device (CCD) camera (Photometrics Ltd., Tucson, AZ, USA). The microscope was equipped with a 470±20 nm excitation filter, a 505 nm dichroic mirror and a 515±15 nm emission filter (Delta Lys & Optik, Lyngby, Denmark). The excitation light source was a 100W HBO arc lamp.

Redistribution of the C-GFP^{LT} fusion protein was quantified using an image analysis program custom written in LabVIEW (National Instruments, Austin, TX, USA). Fluorescent aggregates are segmented from each image using an automatically found threshold based on maximisation of the information measure between the object and the background. The *a priori* entropy of the image histogram is used as the information measure[37]. The area occupied by aggregates in each image is calculated by counting pixels in the segmented areas. The value thus obtained for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image

collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.

Spot photobleaching

A Zeiss LSM 410 with x40 Fluar (as above) was used in spot scan mode at 488 nm to bleach individual fluorescent C-GFP^{LT} aggregates within CHO cells variously treated with forskolin. Fluorescence recovery at the locus of each aggregate was monitored immediately after bleach with successive small-area raster scans just large enough to include most of the cell in which the aggregate lay. Nominal output of the laser at 488 nm, before launch into the microscope, was 10 mW. Subsequent raster scans were also run with the laser at full intensity and without a confocal aperture to allow the first to be made within 0.2 seconds of bleach, and for each scan to be completed within 0.3 seconds (100 x 100 pixels per scan). The recovery of fluorescence for the majority of bleach experiments was measured over a period of 215 seconds, recorded in three consecutive blocks of 10 scans having successive intervals between frames of 0.5, 1 and 5 seconds, and a final set of 15 scans each 10 seconds apart. A single scan collected prior to each bleach exposure served both to establish depth of bleach and to estimate maximum recoverable fluorescence in each experiment. Bleach recovery scans (8-bit images) were analysed using IPlab Spectrum software (Signal Analytics Corp., Vienna, VI, USA). A small region of interest (ROI) of between 6x6 to 10x10 pixels was used to define the area for which fluorescence recovery would be monitored in each experiment, and the average fluorescence within that ROI was measured for successive frames in each time series. The measurement ROIs were slightly larger than the bleached C-GFP^{LT} aggregates to allow for cytoplasmic movements during the measurement period. The total average fluorescence within each frame was also measured to allow fluorescence recovery within C-GFP^{LT} aggregates to be corrected for the minor effects of photobleaching caused by the series of measurement scans.

Results of the spot-bleach experiments are presented as normalised values of displacement from photobleach, $\Delta F(t)$, versus time t:

$$\Delta F(t) = [F(\infty) - F(t)]/[F(\infty) - F(0)]$$

where $F(\infty) = F_i.R_i/R_f$

$F(\infty)$ being the maximum recoverable fluorescence within a measurement ROI calculated from the pre-bleach intensity of the target aggregate, F_i, corrected for total loss of fluorophores within the cell, R_i/R_r, during the bleach exposure and recovery periods.

SPA

CHO/C-GFP^{LT} cells were cultured in HAM's F12 medium as described above, but in 96-well plates. The medium was exchanged with Ca^{2+}-HEPES buffer containing 100 μM IBMX. The cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

Automated imaging

A Diaphot300 microscope (Nikon Corp., Tokyo, Japan) coupled to a camera based on the SITe back illuminated 512 x 512 CCD camera (Princeton Instruments Inc., Trenton, NJ, USA) and integrated with a digital data acquisition system using LabVIEW software was configured to allow automated focusing and image-based analyses in 96-well plates. CHO/C-GFP^{LT} cells were cultured as described above but in 96-well plates and kept at 37°C throughout the experiments. A fluorescence micrograph of the same field of cells, initially chosen at random, was acquired before and 30 min after forskolin stimulation and analysed as described above.

Endomembrane labelling with fluorescently tagged ceramides

Golgi membranes in CHO/C-GFP^{LT} cells were labelled with ceramide-FL (Molecular Probes Inc., Eugene, OR, USA) at 0.5 μM for 20 minutes before washing. Ceramide-FL excited at 480 nm normally emits in the green at about 510 nm, but when concentrated (as in Golgi membranes) the fluorophore forms excimers, resulting in a shift in the emission maximum to greater than 600 nm[38]. Images were collected at both 520 ± 10 nm and beyond 570 nm, allowing good separation of GFP^{LT} and ceramide-FL signals.

Structure of the GFP^{LT}-bright aggregates

Through-focus images of individual C-GFP^{LT} aggregates were collected from chilled cells with a x63 NA 1.4 oil-immersion objective. The built-in focus motor of the Zeiss LSM 410 was used to advance the objective 0.2 μm between images, 25 images per data set. Effective pixel size in the images was 65.6 nm. Data sets were corrected for bleaching and fluctuations in illumination intensity. Out-of-focus information in the images was removed using iterative, constrained, three-dimensional deconvolution (DeltaVision from Applied Precision Inc., Seattle, WA, USA) based on a theoretically calculated point-spread function. The deconvolved images were then reconstructed into a 3-D rotational projection of 40 images (9 degrees between images) using the method of maximum intensity ray-tracing (DeltaVision, Applied Precision, Inc., Seattle, USA). Two adjacent images in this set, re-sized and pixel-smoothed, were used to create the stereo pair shown in Figure 6C. An iso-surface rendering of the 3-D reconstruction was created using Milan software (BitPlane AG, Zurich, Switzerland) (Fig. 6B).

Acknowledgments

We acknowledge Dr. S. P. Bjørn (Novo Nordisk) for developing a mutagenised cDNA clone for the highly fluorescent derivative of green fluorescent protein used in this study, Dr. G. S. McKnight, Howard Hughes Medical Research Institute, Seattle, USA for providing us with his cDNA clone of the Cα subunit of murine cAK and G. Hagel for expert technical assistance.

References

1. Walsh, D.A., Perkins, J.P., and Krebs, E.G. 1968. An adenosine 3',5'-monophosphate-dependant protein kinase from rabbit skeletal muscle. *J. Biol. Chem.* **243:**3763-3765.
2. Taskén, K., Skålhegg, B.S., Taskén, K.A., Solberg, R., Knutsen, H.K., Levy, F.O., Sandberg, M., Ørstavik, S., Larsen, T., Johansen, A.K., Vang, T., Schrader, H.P., Reinton, N.T.K., Torgersen, K.M., Hansson, V., and Jahnsen, T. 1997. Structure, function, and regulation of human cAMP-dependent kinases. *Adv. Second Messenger Phosphoprotein Res.* **31:**191-204.
3. Kingston, P.A., Zufall, F., and Barnstable, C.J. 1996. Rat hippocampal neurons express genes for both rod retinal and olfactory cyclic nucleotide-gated channels: Novel targets for cAMP/cGMP function. *Proc. Natl. Acad. Sci. USA* **93:**10440-10445.
4. Taskén, K., Solberg, R., Foss, K.B., Skålhegg, B.S., Hansson, V., and Jahnsen, T. 1995. *The Protein Kinase Facts Book: Protein-Serine Kinases* (Eds., Hardie, G., and Hanks, S.), Academic Press Ltd., London, UK, pp 58-63
5. Taskén, K., Skålhegg, B.S., Solberg, R., Andersson, K.B., Taylor, S.S., Lea, T., Blomhoff, H.K., Jahnsen, T., and Hansson, V. 1993. Novel isozymes of cAMP-dependent protein kinase exist in human cells due to formation of RIα-RIβ heterodimeric complexes. *J. Biol. Chem.* **268:**21276-21283.
6. Beebe, S.J., Salomonsky, P., Jahnsen, T., and Li, Y. 1992. The Cγ subunit is a unique isozyme of the cAMP-dependent protein kinase. *J. Biol. Chem.* **267:**25505-25512.
7. Gamm, D.M., Baude, E.J., and Uhler, M.D. 1996. The major catalytic subunit isoforms of cAMP-dependent protein kinase have distinct biochemical properties *in vitro* and *in vivo*. *J. Biol. Chem.* **271:**15736-15742
8. Robinson, M.L., Wallert, M.A., Reinitz, C.A., and Shabb, J.B. 1996. Association of the type I regulatory subunit of cAMP-dependent protein kinase with cardiac myocyte sarcolemma. *Arch. Biochem. Biophys.* **330:**181-187.
9. Moos, J., Peknicová, J., Geussová, G., Philimonenko, V., and Hozák, P. 1998. Association of protein kinase A type I with detergent-resistant structures of mammalian sperm cells. *Mol. Reprod. Dev.* **50:**79-85.

10. Nigg, E.A., Schäfer, G., Hilz, H., and Eppenberger, H.M. 1985. Cyclic-AMP-dependent protein kinase type II is associated with the Golgi complex and with centrosomes. *Cell* **41:**1039-1051.

11. Li, Y., Ndubuka, C., and Rubin, C.S. 1996. A kinase Anchor protein 75 targets regulatory (RII) subunits of cAMP-dependent protein kinase II to the cortical actin cytoskeleton in non-neuronal cells. *J. Biol. Chem.* **271:**16862-16869.

12. Pariset, C., and Weinman, S. 1994. Differential localization of two isoforms of the regulatory subunit RIIα of cAMP-dependent protein kinase in human sperm: Biochemical and cytochemical study. *Mol. Reprod. Dev.* **39:**415-422.

13. Shmyrev, I.I., Grozdova, I.D., Kondratyev, A.D., Mamayeva, E.G., and Severin, E.S. 1990. Immunofluorescence localization of the regulatory subunit type II of cAMP-dependent protein kinase in PC12 and 3T3 cells in different proliferative states. *Mol. Cell. Biochem.* **93:**47-52.

14. Zhang, Q., Carr, D.W., Lerea, K.M., Scott, J.D., and Newman, S.A. 1996. Nuclear localization of type II cAMP-dependent protein kinase during limb cartilage differentiation is associated with a novel developmentally regulated A-kinase anchoring protein. *Dev. Biol.* **176:**51-61.

15. Coghlan, V.M., Bergeson, S.E., Langeberg, L., Nilaver, G., and Scott, J.D. 1993. *A-Kinase Anchoring Proteins*: a key to selective activation of cAMP-responsive events? *Mol. Cell. Biochem.* **127/128:**309-319.

16. Huang, L.J.-S., Durick, K., Weiner, J.A., Chun, J., and Taylor, S.S. 1997. D-AKAP2, a novel protein kinase A anchoring protein with a putative RGS domain. *Proc. Natl. Acad. Sci. USA* **94:**11184-11189.

17. Carr, S.A., Biemann, K., Shoji, S., Parmelee, D.C., and Titani, K. 1982. *n*-Tetradecanoyl is the NH_2-terminal blocking group of the catalytic subunit of cyclic AMP-dependent protein kinase from bovine cardiac muscle. *Proc. Natl. Acad. Sci. USA* **79:**6128-6131.

18. Adie, E.J., Thomas, P.H., Munday, M.R., and Clegg, R.A. 1995. Subcellular targeting of recombinant and mammalian Cα subunits of cAMP-dependent protein kinase. *Biochem. Soc. Trans.* **23:**451S.

19. Yang, S., Fletcher, W.H., and Johnson, D.A. 1995. Regulation of cAMP-dependent protein kinase: Enzyme activation without dissociation. *Biochemistry* **34:**6267-6271.

20. Hardie, D.G. 1991. *Biochemical Messengers: Hormones, Neurotransmitters and Growth Factors*, Chapman & Hall, London, UK
21. Harootunian, AT., Adams, SR., Wen, W., Meinkoth, J.L., Taylor, S.S., and Tsien, R.Y. 1993. Movement of the free catalytic subunit of cAMP-dependent protein kinase into and out of the nucleus can be explained by diffusion. *Mol. Biol. Cell* **4:**993-1002.
22. Nigg, E.A., Hilz, H., Eppenberger, H.M., and Dutly, F., 1985. Rapid and reversible translocation of the catalytic subunit of cAMP-dependent protein kinase type II from the Golgi complex to the nucleus. *EMBO J.* **4:**2801-2806.
23. Walsh, D.A., and Van Patten, S.M. 1994. Multiple pathway signal transduction by the cAMP-dependent protein kinase. *FASEB J.* **8:**1227-1236.
24. Mellon, P.L., Clegg, C.H., Correll, L.A., and McKnight, G.S. 1989. Regulation of transcription by cyclic AMP-dependent protein kinase. *Proc. Natl. Acad. Sci. USA* **86:**4887-4891.
25. Hagiwara, M., Brindle, P., Harootunian, A., Armstrong, R., Rivier, J., Vale, W., Tsien, R., and Montminy, M.R. 1993. Coupling of hormonal stimulation and transcription via the cyclic AMP-responsive factor CREB is rate limited by nuclear entry of protein kinase A. *Mol. Cell. Biol.* **13:**4852-4859.
26. Adams, S.R., Harootunian, A.T., Buechler, Y.J., Taylor, S.S., and Tsien, R.Y. 1991. Fluorescence ratio imaging of cyclic AMP in single cells. *Nature* **349:**694-697.
27. Elson, E.L., and Qian, H. 1989. Interpretation of fluorescence correlation spectroscopy and photobleaching recovery in terms of molecular interactions. *Methods Cell Biol.* **30:**307-332.
28. Lipsky, N.G., and Pagano, R.E. 1985. A vital stain for the Golgi apparatus. *Science* **288:**745-747.
29. Knighton, D.R., Zheng, J., Ten Eyck, L.F., Ashford, V.A., Xuong, N.-h., Taylor, S.S., and Sowadski, J.M. 1991. Crystal structure of the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. *Science* **253:**407-414.
30. Knighton, D.R., Zheng, J., Ten Eyck, L.F., Xuong, N.-h., Taylor, S.S., and Sowadski, J.M. 1991. Structure of a peptide inhibitor bound to the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. *Science* **253:**414-420.

31. Scott, J.D. 1991. Cyclic nucleotide-dependent protein kinases. *Pharmacol. Ther.* **50:**123-145.

32. Skålhegg, B.S., Keryer, G., Torgersen, K.M., Aandahl, E.M., Levy, F.O., Jahnsen, T., Hansson, V., and Taskén, K. 1997. Function and localization of cAMP-dependent protein kinase type I and II in lymphoid cells. *FEBS special meeting 1997: Cell signalling mechanisms*, Elsevier Science, The Netherlands, Abstract P6-123

33. Akey, C.W. 1995. Structural plasticity of the nuclear pore complex. *J. Mol. Biol.* **248:**273-293.

34. Uhler, M.D., Carmichael, D.F., Lee, D.C., Chrivia, J.C., Krebs, E.G., and McKnight, G.S. 1986. Isolation of cDNA clones coding for the catalytic subunit of mouse cAMP-dependent protein kinase. *Proc. Natl. Acad. Sci. USA* **83:**1300-1304.

35. Sambrook, J., Fritsch, E.F., and Maniatis, T. 1989. *Molecular Cloning: A Laboratory Manual, 2nd Ed.*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA

36. Bradford, M.M. 1976. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* **72:**248-254.

37. Kapur, J.N., Sahoo, P.K., and Wong, A.K.C. 1985. A new method for gray-level picture thresholding using the entropy of the histogram. *Computer Vision, Graphics, and Image Processing* **29:**273-285.

38. Haugland, R.P. 1996. *Handbook of fluorescent probes and research chemicals,* 6th Ed. Molecular Probes, Oregon, USA, p281.

Figure legends

Table 1. Time from initiation of a response to half maximal ($t_{1/2max}$) and maximal (t_{max}) C-GFP^{LT} redistribution. The data was extracted from curves such as shown in Figure 3B. All $t_{1/2max}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

Figure 1. Western blot analysis of lysates containing C-GFP^{LT} fusion proteins. Total lysates of BHK/GR,C-GFP^{LT} (A) and control BHK/GR (B) cells were probed with an anti-Cα antibody. 500 ng of purified bovine C subunit (C) was included as a positive control and to identify the endogenous C subunit. Although the antibody clearly reacts unspecifically with several proteins in the total lysates, the fusion protein (f) is recognised as a specific band, migrating with an apparent size of 60 kDa, in the transfected cells (A). The endogenous C subunit (e) migrated as predicted by its molecular weight of 41 kDa. It is possible to compare the expression levels of endogenous hamster C subunit and overexpressed mouse fusion proteins in these blots since the immunogenic peptide is conserved between these two species.

Figure 2. Fluorescence micrographs of CHO cells expressing C subunit fusion proteins. The two fusion proteins of the C subunit of cAK show distinct localisation patterns. A. The NH_2-terminal GFP^{LT}-C fusion protein is localised almost evenly throughout the cytoplasm. B. The COOH-terminal C-GFP^{LT} fusion protein is highly concentrated in cytoplasmic aggregates, often in one large and several minor structures per cell. Scale bar 10 μm.

Figure 3. Time-lapse analyses of fluorescence redistribution in CHO/C-GFP^{LT} cells treated with various agonists. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of agonist. Six of these images are shown (A) for the typical response to 1 μM forskolin, taken at the time points indicated. The time point t=0 corresponds to the image acquired immediately before the cells were challenged with agonist. Scale bar

10 μm. The charts (B-G) each show a quantification of the responses in each time series. The total area of the highly fluorescent aggregates (see Experimental Protocol) is plotted versus time for each experiment. (B) Redistribution time profiles of the C-GFP^{LT} fusion following treatment of cells with various concentrations of forskolin. (C) Response following addition of 1 mM dbcAMP. (D) The effect of 100 μM IBMX on the fusion protein distribution. (E) Demonstrates the reversibility of the forskolin-induced redistribution of C-GFP^{LT}, where 10 μM forskolin (open arrow) is followed shortly by repeated washings with buffer (dark arrow). In a parallel experiment, treatment with 10 μM forskolin plus 100 μM IBMX is followed by repeated washing with buffer containing 100 μM IBMX. (F) BHK/GR,C-GFP^{LT} cells treated with 100 nM glucagon. (G) CHO/C-GFP^{LT} cells transiently transfected with the ARα2a were pretreated with 10 μM forskolin (open arrow) to increase $[cAMP]_i$ then given 10 μM norepinephrine in the continued presence of forskolin.

Figure 4. (A) Four frames from the recovery sequence following spot photobleach of a large aggregate (arrow) in a CHO/C-GFP^{LT} cell exposed to 25 μM forskolin. Times are seconds after bleach. (B) Normalised displacement curves of the fluorescence recovery process in cells exposed to various levels of forskolin. Measurement points are averages±sem (n=4). (C) Linear fits to the first five points of the normalised recovery curves shown in (B). The slope of each line is used as an estimate of the half-time of recovery from bleach at each forskolin concentration.

Figure 5. Parallel dose response analyses of forskolin effects in CHO/C-GFP^{LT} cells on: $[cAMP]_i$ elevation (□), the rate of recovery from spot photobleach (Δ) and induced change in C-GFP^{LT} redistribution (•). $[cAMP]_i$ was measured by SPA assay, analysing the effects of buffer or 8 increasing concentrations of forskolin in these cells. The graph shows a trace of the mean±sem expressed in arbitrary units (n=4 for each data point). Half times for recovery from spot photobleach were estimated from the first 5 time points of the mean value (n=4) curves in Figure 4B. Changes induced in C-GFP^{LT} distribution were quantified as described (Experimental Protocol) using fluorescence micrographs taken of the same field of cells prior to and 30 min after the addition of forskolin. The graph shows a trace of the mean±sem at each forskolin concentration (n=8 for each data point). The fitted curves indicate ½-maximal concentration values for

forskolin as: 1.7 μM, image-based assay (□); 3.0 μM, spot photobleach assay (Δ); 9.3 μM, SPA (●).

Figure 6. (A) Two images of CHO/C-GFP^{LT} cells stained with ceramide-FL, in emission ranges of 520 ± 10 nm and >570 nm, have been superimposed to demonstrate the distinct separateness of Golgi membranes (orange) and C-GFP^{LT} fluorescence (green). Scale bar is 10 μm. (B) An iso-surface rendering of a single large C-GFP^{LT} aggregate (similar to that arrowed in 6A). The image is a reconstruction from 25 through-focus images deconvolved and processed as described (Experimental Protocol). Scale bar 1 μm. (C) Stereo pair of the reconstructed images used to generate the iso-surface seen in (B). Each image is smoothed for presentation, the structure originally being 35 pixels high by 27 wide in this orientation. Scale bar 1 μm.

Figure 1

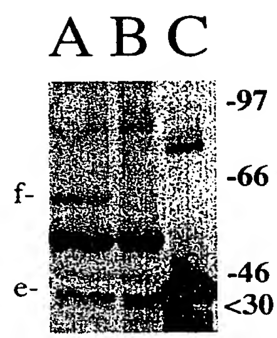


Figure 2

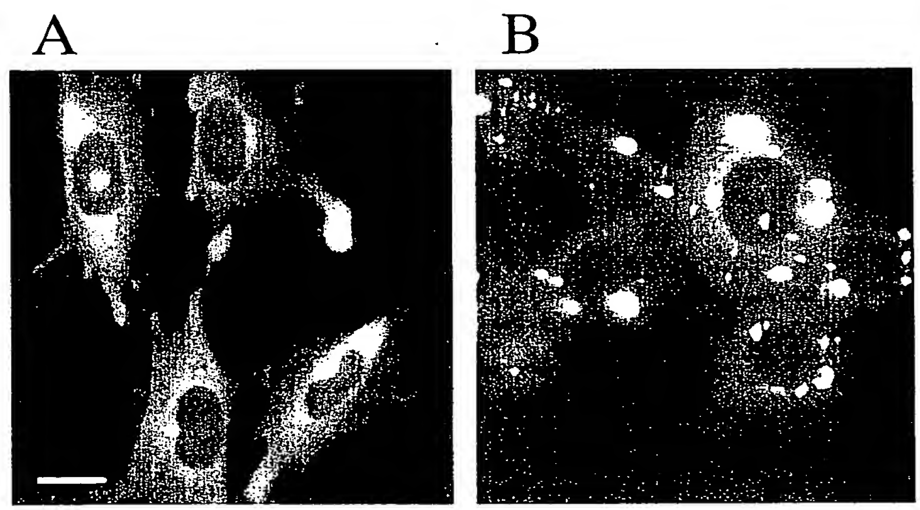


Figure 3

A

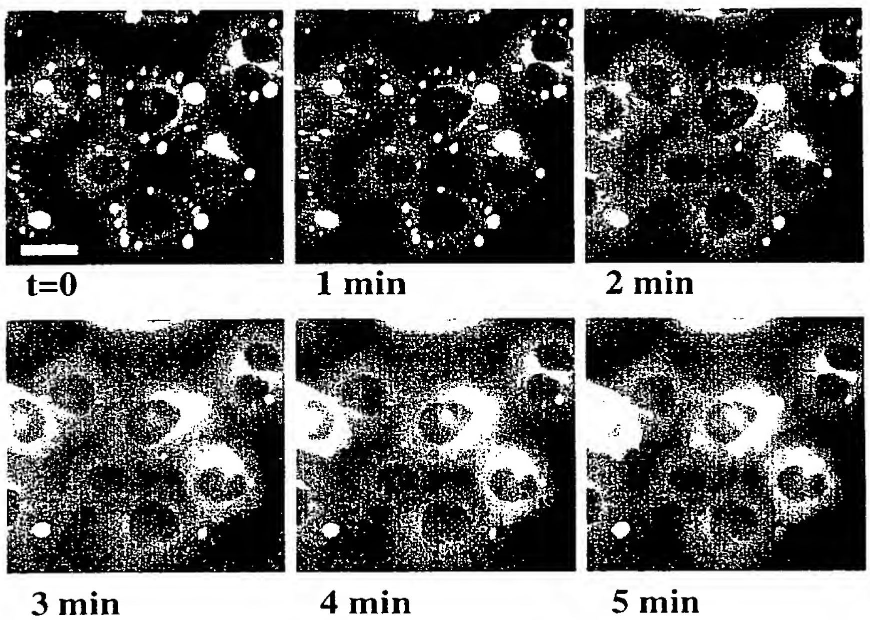
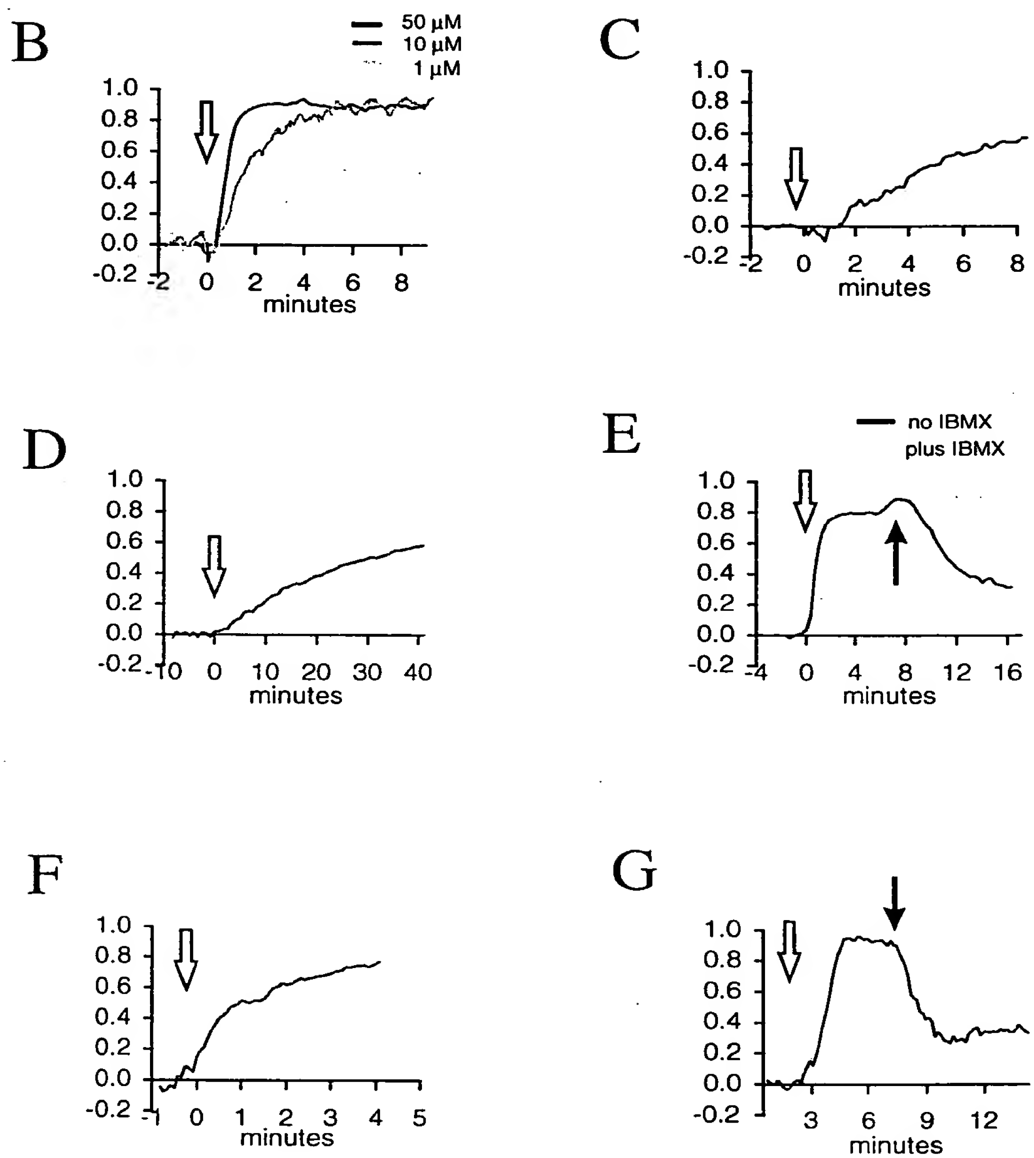


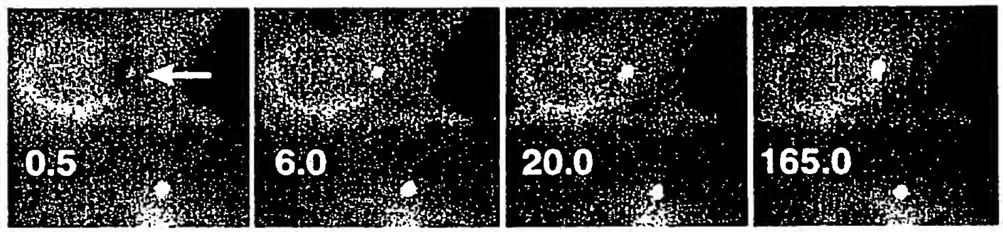
Figure 3


B
50 µM
10 µM
1 µM
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-2 0 2 4 6 8
minutes
C
-2 0 2 4 6 8
minutes
D
-10 0 10 20 30 40
minutes
E
no IBMX
plus IBMX
-4 0 4 8 12 16
minutes
F
-1 0 1 2 3 4 5
minutes
G
3 6 9 12
minutes

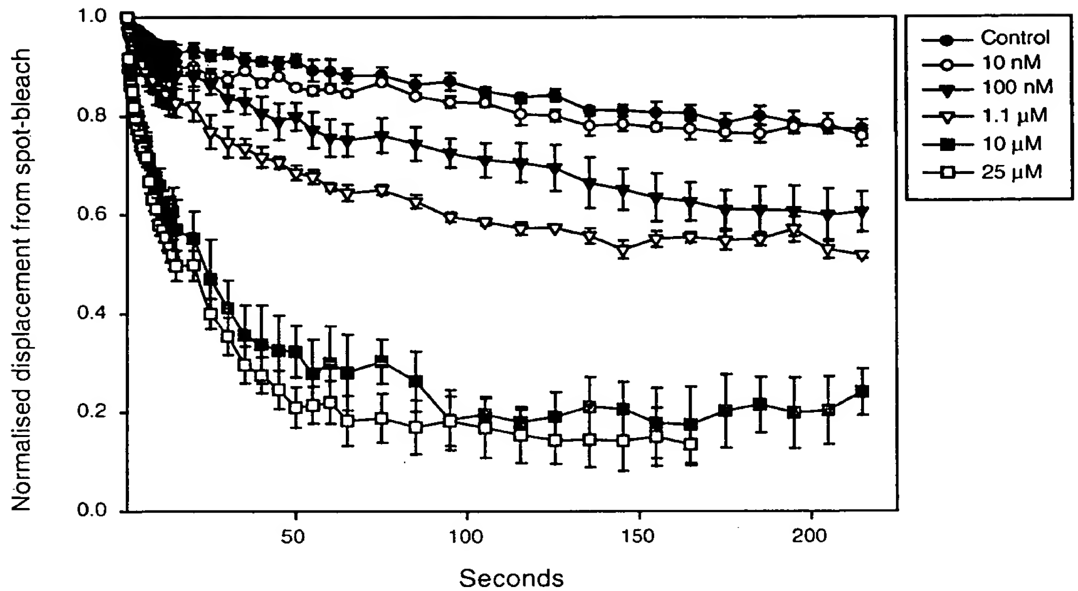
Modtaget PD
15 OKT. 1998

Figure 4

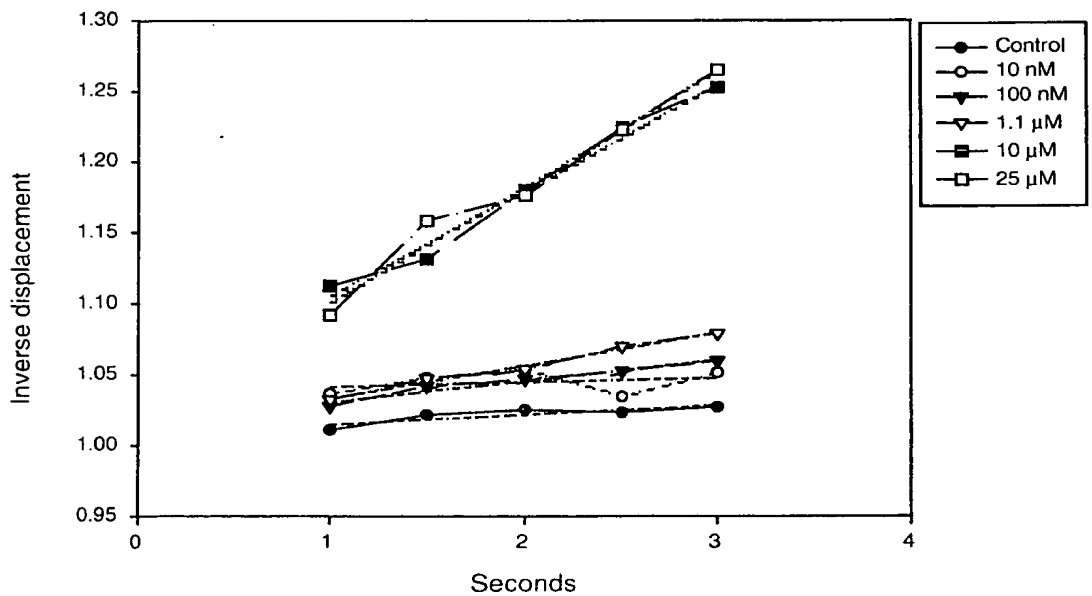
A



B



C



22129DK1 Appendix I

Figure 5

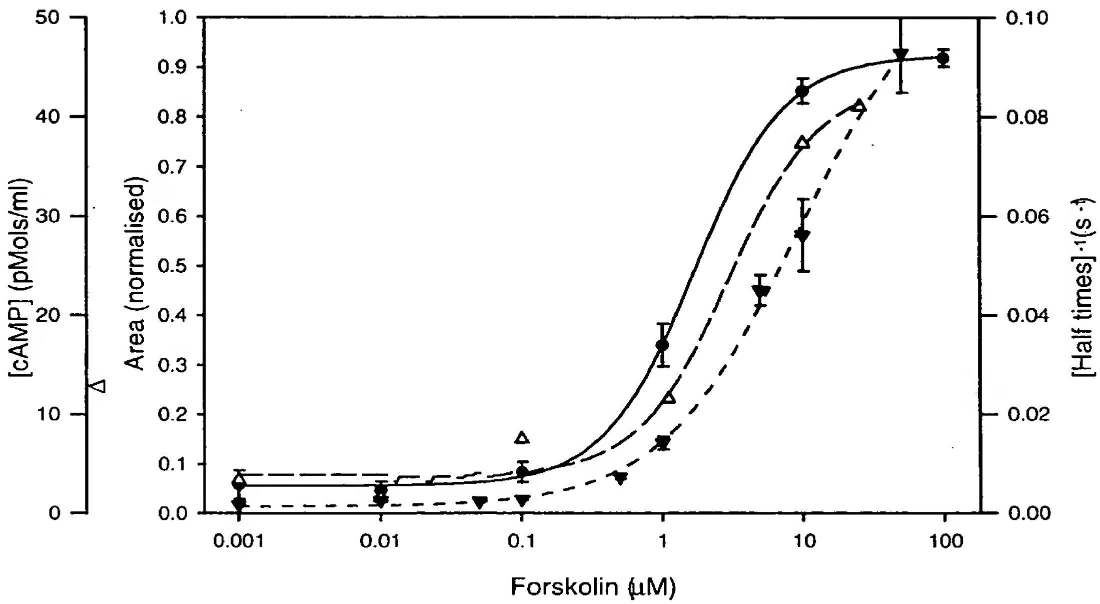

50
40
30
20
10
0
[cAMP] (pMols/ml)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Area (normalised)
0.10
0.08
0.06
0.04
0.02
0.00
[Half times]-1(s-1)
0.001
0.01
0.1
1
10
100
Forskolin (µM)

Figure 6

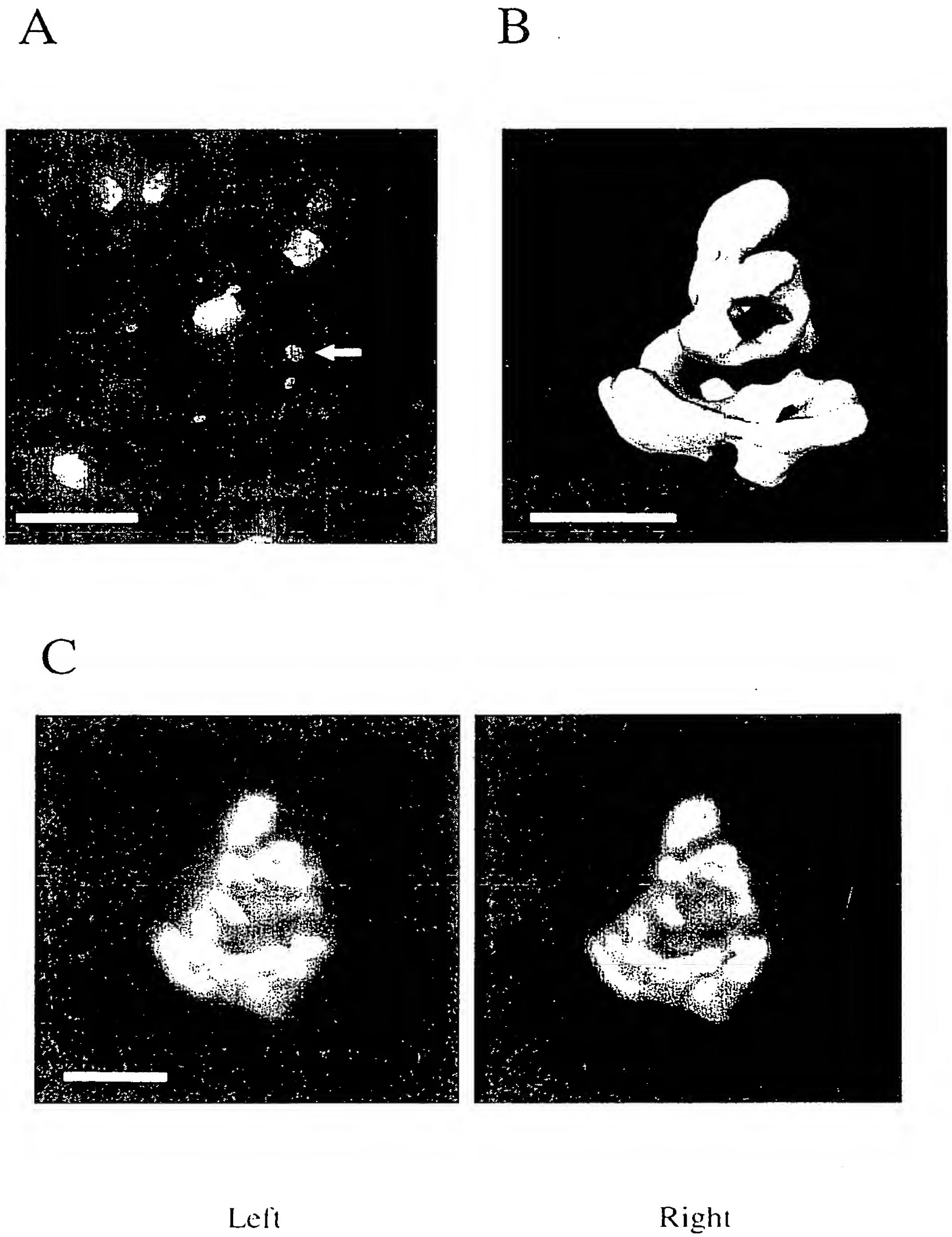


Table 1

[forskolin]/μM	$t_{1/2max}$ / s	t_{max} / s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

Attorney Docket No. 5441.003

METHOD AND APPARATUS FOR HIGH DENSITY FORMAT SCREENING FOR BIOACTIVE MOLECULES

FIELD OF THE INVENTION

The invention relates to a method and apparatus for screening large numbers of molecules for biological activities.

BACKGROUND OF THE INVENTION

Current technology is able to generate large numbers of molecules which may possess potential therapeutic value. Compounds having potentially interesting biological activity may be products of combinatorial or traditional chemistry, a natural product, proteins isolated by one- or two-dimensional gel electrophoresis, or compounds secreted from or expressed by natural or genetically modified animal, plant, microbial or fungal cells (or parts thereof), or displayed by natural or genetically modified viral or phage particles.

Screening methods have been developed which achieve very high throughputs of test compounds. Such methods are termed Ultra High Throughput Screening (UHTS). The present generation of UHTS machines rely upon essentially serial additions of test compounds, usually one test compound per discrete test well. Test well array densities range from between 96 to 3456 wells per plate. Such UHTS machines require sophisticated technologies to dispense microvolumes of many different fluids to selected locations, and also require that the detecting surface for each test molecule generally be separated from other detecting surfaces within the array.

There is a need to develop a method which allows simultaneous screening of large numbers of test compounds for biological activity and potential therapeutic use while avoiding the complications associated with dispensing multiple fluid microvolumes.

BRIEF SUMMARY OF THE INVENTION

The invention is directed to a screening method which eliminates the need for delivering microfluid volumes and allows simultaneous parallel screening of large numbers of test compounds. Accordingly, the invention is drawn to a method for screening test

compounds for bioactivity, by contacting an array of test compounds with a detector layer capable of detecting bioactivity, wherein a cell response is indicative of bioactivity.

The method of the invention is a high throughput system for parallel screening of a large number of test compounds. In one embodiment of the method of the invention, 96 to 10,000 test compounds are simultaneously screened for bioactivity in an assay; in a more specific embodiment, 96 to 3456 test compounds are simultaneously screened for bioactivity.

In a more specific embodiment, invention is drawn to a method for screening test compounds for bioactivity, comprising:

(a) contacting a solid support comprising an array of test compounds with a liquid layer, wherein the liquid layer is in immediate contact with a detector layer and wherein each test compound comes into contact with a localized portion of the liquid layer; and

(b) registering a response of the detector layer to the test compound, wherein a bioactive test compound is identified.

By "high throughput screening" is meant a method able to screen large number of test compounds for biological activity within a given machine time (i.e. at a rate anywhere from 100 to 100,000 compounds per hour per machine).

The term "parallel screening" refers to a method by which very many compounds are applied simultaneously to the detector layer, and similarly, signals from that detector layer are collected contemporaneously rather than sequentially.

By "array" is meant a regular two-dimensional arrangement of test compounds by which compounds are disposed at the nodes of a rectilinear grid pattern whereby a compound position can be identified by a simple 2-dimensional coordinate.

A "detector layer" means any two-dimensional system which can be used to report biologically relevant information. In one specific embodiment of the method of the invention the detector layer is a monolayer of living cells loaded with a fluorescent reporter dye such as Fluo-3.

By "bioactive" or "bioactivity" is meant an action or influence of a test compound upon the detector layer which results in a response from the detector layer that has direct biological significance or can be interpreted as being a biologically relevant response. Bioactive agents have the ability to effect physiological parameters of living cells and tissues. Bioactivity includes inducing or suppressing the expression of a protein, activating or inhibiting transcription of a gene, and/or effecting cellular function(s) such as, for example,

intracellular movement and storage of calcium ions, and membrane transportation.

The capacity of a test compound to affect a detector layer, i.e. bioactivity, may be determined in a number of ways known to the art. In specific embodiments of the method of the invention, bioactivity is determined by changes or movements of fluorescent probes present in the detector layer which indicate changes in ionic content, cell metabolism, growth or viability. In a preferred method of the invention, living cells form the detector layer and have specific protein components tagged with a fluorescent agent, such as green fluorescent protein (GFP); changes in GFP fluorescence or distribution within cells indicate a particular cellular response which may be selected for identification of bioactivity.

The phrase "a change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarization.

A "solid support comprising an array of multiple test compounds" or similar terms, mean a fixed matrix to which test compounds have been fixed. As an example, the solid support of the invention includes a membrane or other surface comprising an array of printed test compounds. In one specific embodiment of the invention, the test compounds are deposited as discrete spots on a porous track-etched polycarbonate membrane 10 to 20 microns thickness, the spots being between 10 microns to 2 mm diameter. The quantity of compound contained in each discrete spot will depend on the concentration of the stock solution from which it was derived, and the volume of that stock solution applied to the support. In another specific embodiment of the invention, compounds are printed onto a non-porous solid support which is optically clear.

By "test compounds" is meant a fixed array of compounds to be screened for ability to effect physiological parameters of a cell or tissue. In one embodiment, the test compounds are proteins or peptides generated by combinatorial protein chemical methods known to the art. In another embodiment, the test compounds are chemical compounds generated by combinatorial chemistry methods known in the art. In another embodiments, the test compounds are chemical compounds which are naturally occurring compounds more or less purified from their native state, are the products of genetically engineered cells, or are viral or bacteriophage particles engineered to display compounds upon their surfaces (phage display).

In one embodiment, the detector layer is an undemarcated area of living cells growing on a flat culture surface. The cells on this surface may or may not be grown to confluence,

may be transformed and/or engineered cells, or directly derived from animal tissues and grown as primary cell culture.

In one embodiment, a test compound reaches the detector layer by diffusion through a porous membrane to a liquid layer immediately overlaying the detector layer. A variety of commercially available porous membranes are useful in the method of the invention. A preferred porous membrane is a track-etched polyester or polycarbonate support in which parallel channels of identical size are formed by a selective etching process following exposure of the membrane to a source of high energy ions. The method of the invention allows each test compound affixed to a solid support to come into contact with a limited fluid volume, which fluid volume is in immediate contact with the detector layer. In one embodiment, each test compound contacts the detector layer by diffusion through a liquid-containing channel directly adjacent to the detector layer.

One advantage of the method of the invention is that it allows massive parallel screening of a large array of test compounds for biological activity. When living cells are the detector layer of the invention, they are maintained under physiologically viable conditions. Provision of these conditions requires the use of solutions able to supply essential nutrients and buffer pH changes normal to the continued growth of living cells. Such solutions may be complete cell culture media (i.e. any of those commercially available, for instance from Life Technologies Ltd.), optionally supplemented with antibiotics and serum preparations for optimal cell growth conditions. Buffer solutions may also be of the type known as "chemically defined". Cells will also require controlled temperature conditions, in the range 20° to 37°C, and the provision of gases essential to continued cell growth and maintenance of buffer capacity (O_2, and optionally 5% CO_2, depending on the type of buffer being used).

These and other objectives, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the method as more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing features of the present invention may be fully understood from the following detailed disclosure of a specific preferred embodiment in conjunction with the accompanying drawings in which:

Fig. 1 is a schematic representation of the apparatus useful in one specific embodiment of the invention: Light from a high energy light source **1** is collected and collimated by unit **2**, directed through a shutter assembly **3** and passes through a excitation filter-changer **4**. A light guide **5** directs excitation light into the lensing and epi-illumination optics housed in unit **7**. Excitation light emerging from **7** illuminates the horizontal detector layer located in the multi-component assembly having two solid layers **10** and **11** fixed relative to a supporting stage unit **8**. Layer **11** is moved vertically downward on guide pins **(17** Fig. 2b**)** controlled by arm **12** driven by unit **13**. Four sprung contacts **14** attached to **12** press upon the frame of layer **11** to drive it downwards as arm **12** descends. Specified devices **(3, 4, 9, 13, 15, 16)** are controlled by central processing unit **6** which issues commands and collects data and status information from the devices attached to it. Unit **6** includes a central processing unit, RAM, multi-channel serial input/output cards with onboard A/D and D/A converters, one of which cards controls the camera **16** and captures images from it.

Figs. 2a-c: Figs. 2a and 2b are side view of the test stage (not to scale); Fig. 2c is a top view of the test stage. A supporting stage **8** has a rectangular central aperture the shape and size of which is the same as the area **19** of Fig. 2c. The position of stage **8** is adjusted in the horizontal and vertical axes by the 3-axis positioner **9**. Components of the test stage shown include, solution layer **18**, (not shown: detector layer **20** and array of test compounds **21** in Figs 3 and 4). The array **21** is held away from the liquid layer by pins **17** which pass through holes (**24** in Fig. 5) in the corners of the frame **11**. Arm **12** is moved down by the drive unit **13,** and the four sprung contacts **14** it bears exert pressure on the frame **11** moving it down the guide pins **17** and into close proximity to the upper surface of **10,** from which it is separated by a thin liquid layer **18**.

Fig. 3 is a schematic showing the relative positions of the different layers in the test-array/detector layers used in one specific embodiment. The layers are depicted in apposition, as they would appear after arm **12** has pushed component **11** down the support pins **17**. An array of discrete spots of test compounds **21** on a porous membrane **19** is in contact with a liquid layer **18** overlaying the detector layer **20** which is supported by an optically transparent

solid substrate **10**. The compounds fill the parallel capillary spaces in the track-etched membrane **22**.

Fig. 4 is a schematic drawing of a second embodiment of the screening method of the invention. The layers are depicted in apposition, as they would appear after arm **12** has pushed component **11** down the support pins **17**. A detector layer **20** supported on an optically clear porous membrane **19**, and overlayed by a liquid layer **23**, is placed onto an optically clear solid substrate **10** bearing an array of test compounds **21**. The thin space **18** between components **19** and **10** is filled with solution from **23** which has passed through the porous membrane **19**. Bioactivity is detected by measuring changes in fluoresence of the detector layer resulting from responses to the diffusion of test compounds through the porous membrane to the detector layer.

Figs. 5a-c are schematics illustrating transfer printing of an array of compounds onto a surface of a track-etched membrane. Compounds are stored in 16 separate 96-well microtitre plates and defined amounts are transferred simultaneously by a 96-pin printing head to the surface **19** (Fig. 5a). The contents of each successive 96-well plate are printed at a slightly offset position, generating an array after 4 such printing operations (Fig. 5b), and a full array of 1536 compounds after 16 printing operations (Fig. 5c).

DETAILED DESCRIPTION

Before the present method and solutions used in the method are described, it is to be understood that this invention is not limited to particular methods, components, or solutions described, as such methods, components, and solutions may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and

materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

Generally, the invention is drawn to a method for high throughput screening of test compounds, by contacting a solid support comprising an array of multiple test compounds with a detector layer, wherein each test compound comes into contact with a localized liquid which is in contact with a detector layer, and detecting a response of the detector layer to the test compound, wherein a bioactive test compound is identified.

The high density format screening system (HDFS) of the invention, rests in part on the realization that the delivery of test compounds to detector surfaces can be greatly simplified by doing away with the need for complicated microfluidics. Test compounds are applied to the detector surface in a massively parallel manner, and the method is applicable to a large range of different types of test compounds.

Central to the specific embodiments of the method and apparatus of the invention, described below, is the use of living cells as detectors, their responses being signalled via changes in the fluorescent or luminescent properties of various specific probes located within. However many different types of detector systems could be used in place of cells in such a system, for example, appropriate variants of Scintillation Proximity Assay (SPA) systems (Amersham Pharmacia Biotech) and enzyme-linked immuno-sorbent assay (ELISA) systems (Amersham).

Test Compound Arrays

The array of test compounds is formatted to have the same dimensions as the detector surface. In one specific embodiment of the invention, array and detector layers have a width of 8 cm and length of 12.5 cm, so as to fit within the format of conventional 96-well or 384-well microtiter plates. Preparation of the test arrays will depend on their origin.

Test compounds held in formatted arrays. Current methods for the production of single compounds by combinatorial methods are under development which involve miniaturization and patterned arrays of tethered solid-phase substrates. Thus, test compounds generated by combinatorial methods can be used to synthesize an array directly or indirectly on a carrier sheet. In one embodiment, vapor phase solubilization is used to produce a test compound array on the synthetic substrate, followed by a printing process of the test

compound array on to an absorbent membrane. In this embodiment, the test array is the printed membrane. An attractive feature of this method is that multiple copies of the same test array can be produced at one time to be screened against multiple cell systems for specific activities which minimizes stock handling from library archives.

Currently most compounds to be screened come in 96-well format. However, the 96-well format can be altered by repeated off-set printings, to any chosen density of format that the transfer substrate and assay can support. The optimum density of compounds in the test array will depend very much on the fraction of compounds in an array which generate bioactive responses in the detector layer ("hit rate"). The hit rate will depend on how well the compound library being tested matches the targets in the assay. If the hit rate is low, e.g., 1:20,000 - 100,000 compounds tested, a test array with center to center spacing of 200 μm (giving 240,000 separate compounds in a 12 cm x 8 cm area) may be preferable, providing 2 to 10 hits per plate. At a spacing of 1 mm, 9,600 test compounds may be screened simultaneously.

The density of the format may be adjusted as required without requiring any changes in the hardware used to perform the re-formatting; rather, adjustment may be made in the degree of off-set and the number of print operations used per array.

Detection

Fluorescent imaging provides a way to monitor physiological responses of living cells in a non-invasive manner. Ion- and voltage-sensitive probes, as well as the new generation of recombinant fluorescent probes, for instance, hybrid proteins comprising fusions of green fluorescent protein variants (GFPs) to cellular proteins involved in intracellular signaling, can be used singly or in combination to report on many aspects of cellular microphysiology. Due to the strong fluorescence of GFP, the luminescence of cells expressing the probes may easily be detected and analyzed by employing a combination of fluorescence microscopy and image analysis. Furthermore, these probes described are easily introduced into cells, as they can be expressed in the cells of interest after transfection with a suitable expression vector.

Recombinant probes for second messengers and enzyme activity, such as kinase activity, are not only useful in basic research but also in screening programs aiming at identifying novel biologically active substances. As an example, any currently used screening program designed to find compounds that affect cAMP concentration and protein kinase

activity are based on receptor binding and/or immuno detection and/or reporter gene expression. The recombinant probes described herein, on the other hand, make it possible to develop an entirely new types of screening assays able to monitor immediate and transient changes of cAMP concentration and protein kinase activity in intact living cells.

The HDFS method of the invention monitors the response of cell populations to test compounds. Lens systems are currently available which can simultaneously epi-illuminate and image the fluorescence from areas in excess of 8.5 x 13 cm, the size of a standard 96-well plate. The detection method used herein collects a variety of fluorescent signals from all cells in a field, with responses from discrete areas of the field being apparent in the real image of the fluorescence from that field as formed on the surface of the photosensitive detector (imaging camera).

Delivery of Test Compounds to Detector Cells

In a first embodiment of the method of the invention, delivery of large arrays of test compounds to cells is achieved with test compounds which are present on or transferred to a porous carrier sheet. In specific embodiments, test compounds are printed on the carrier sheet, and the sheet is applied (overlayed) to a field of cells of the same area. The test compounds reach the detector cells by diffusion through a localized buffer layer immediately in contact with an area of the detector cell layer. This embodiment is shown in the schematic of Figs. 2 & 3.

Porous carrier sheet for delivery of test compounds: Test compound arrays are fixed onto the porous carrier sheet by a variety of methods known to the art. For example, an array of test compounds may be transferred and fixed to the carrier sheet by the method of contact printing, whereby an array of inert flat-ended pins (e.g. made of stainless steel) is used to transfer defined volumes of individual test compounds (in the range 50 nl to 2 μl) in solution form to discrete points on a dry carrier sheet.

A porous membrane useful in the delivery of test compounds is a membrane constructed of a non-absorbent material with pores of regular and defined diameter which traverse the membrane directly from the upper to the lower side. The property of orthogonal capillarity is useful in these membranes to limit lateral spread of test compounds applied to the membranes as discrete spots of liquid, since it is important that the compounds remain as discrete spots upon the membrane. A variety of membranes of different thicknesses,

materials, and pore densities are commercially available from a number of manufacturers. For example, porous membranes useful in the method of the invention include a track-etched polycarbonate or polyester membrane (Corning Costar or Whatman/Polyfiltronics). These are available in thicknesses from 6 to 23 microns, with pores of 14 to 0.015 microns, at 100,000 to 1,000,000,000 pores/cm^2. For delivery of test compounds with maximum ease of handling and loading of test compounds, polycarbonate membranes are preferred, particularly of a thickness of greater than 10 microns, with pores between 1 and 10 microns diameter at densities of between 20,000,000 to 100,000 pores/cm^2, respectively. One preferred membrane is Nucleopore® from Corning Costar.

Alternative membranes useful for the delivery of compounds include cast cellulose acetate (Membra-fil®), PTFE membranes (e.g. Filinert™), and glass fiber filters, all available from Corning Costar. These thicker membranes encourage lateral spread of liquid samples applied to their surfaces, but are thicker and could thus be used to deliver larger amounts of compounds.

Track-etched and cast cellulosic membranes may also be given hydrophilic or hydrophobic surface treatments. It is useful to have membranes whose surfaces have defined wettability properties.

When the test compound is soluble, the compound will dissolve into the buffer upon contact with the buffer medium, and directly contact the detector layer immediately underlying the buffer layer. In this embodiment, the test compounds dissolve upon contact with the buffer medium, and fall vertically onto the detector layer as a result of having a higher density than the surrounding liquor. It is generally preferred that the thin buffer layer between the test compound membrane and detector layer not be stirred significantly by convection. At the detector layer, the vertical fall of a solution of test compound is expected to spread radially by displacement and diffusion. The radial extent of a measured response may thus be use as an indicator of the bio-potency of the compounds involved.

Test compounds of limited solubility, such as those expressed on the surface of a carrier system, for instance, a cell membrane, viral or phage particle, must be brought into very close proximity, including direct contact, with the detector layers.

Buffer and Detector layer. The detector layer may be a continuous or non-continuous layer of living cells. In a specific embodiment, the detector layer is a continous cell monolayer corresponding in size to the test compound array. In more specific embodiments,

thin glass substrate, suitably tissue culture treated is preferred for fluorescent probes requiring excitation wavelengths below 400 nm.

Living cells are maintained under physiologically viable conditions, as defined by such parameters as oxygen consumption, membrane potential, mitochondrial potential and cytoplasmic ion balance. Provision of these conditions requires the use of solutions able to supply essential nutrients and buffer pH changes normal to the continued growth of living cells. Such solutions may be complete cell culture media (i.e. any of those commercially available, for instance from Life Technologies Ltd.) optionally supplemented with antibiotics and serum preparations for optimal cell growth conditions. Buffer solutions may also be of the type known as "chemically defined" (e.g. phosphate buffered saline solutions). Cells will also require controlled temperature conditions, in the range 20° to 37°C, and the provision of gases essential to continued cell growth and maintenance of buffer capacity (O_2, and optionally 5% CO_2, depending on the type of buffer being used).

Detection of bioactivity. Detection of bioactivity may be determined by a number of methods known in the art. In a preferred embodiment, detection of bioactivity is determined by cellular imaging of fluorescence. For example, imaging may be conducted of a cell layer on a clear glass substrate. A glass substrate having a surface pitted with a regular array of very shallow (approx 20 μm) depressions may be used for this purpose (Corning). This glass substrate is useful because it ensures a regular and defined spacing between the overlying test array and the cells beneath.

In one embodiment, the detector layer is an undemarcated area of living cells growing on a flat culture surface. The cells on this surface may or may not be grown to confluence, may be transformed and/or engineered cells, or directly derived from animal tissues and grown as primary cell culture. In a second embodiment of the method of the invention, the array of test compounds is laid out onto a non-porous substrate (such as thin coverglass sheet) which is transparent or optically clear. Imaging will be through this surface, and through the cell support membrane lying above. The substrate (Fig. 4, **10**) should be inert and solvent tolerant. For example, borosilicate glass sheets of about 200 microns thickness, which may be further surface-treated to give either hydrophobic or hydrophilic properties as desired. This embodiment is shown in the schematic of Fig. 4.

Detector layer: In one embodiment of the invention, the detector layer is a layer of

living cells cultured on a thin porous membrane. A porous membrane useful in the culture and transfer of cells is a transparent non-absorbent membrane with pores of regular and defined diameter which traverse the membrane directly from the upper to the lower side. A porous sheet suitable for cell growth is a track-etched polyester membrane about 10 microns thick with pores between 0.015 and 5 microns diameter at densities of between 600,000,000 to 400,000 pores/cm^2 repectively (Nucleopore® from Corning Costar).

Delivery of test compounds to detector layer. The porous membrane which supports the detector layer, complete with the buffer medium which overlays it, is applied onto the (dry) test array. Buffer medium wets the lower surface of the porous membrane (Fig. 4, **19**) and forms a continuous thin film **23** between the array of test compounds **21** and the porous membrane **19**. Test compounds diffuse up through the pores to the detector layer above. In one embodiment of the invention the detector layer is a monolayer of living cells overlayed with physiological buffer solution. The invention includes the possibility that under some conditions it is desirable to have cells grow processes through the membrane to make direct contact with substances on the test array below, with the use of a membrane having an appropriate pore diameter.

Further embodiments and general considerations. Where a test array is generated as a complex mixture of components, such as from the "teabag" method of combinatorial synthesis, or from cDNA library expression systems, a separation step may first necessary. Separation of test components may be conducted in any number of ways known to the art. In one embodiment, components may be separated by the use of one- or two-dimensional separation techniques in non-denaturing gels. The resulting gels may be used directly as test arrays.

Specific separation methods will be tailored to the components involved. Any bioactive compounds from such an array would be identified from identical copies of the original test gel.

Detection of Bioactivity.

Lens and illumination system. Specialized light sources and optics are needed to illuminate and image the fluorescence coming from an area the size of a microtiter plate (96-well plate). Such a system is available from: Imaging Research Inc., St Catherines, Ontario, Canada, and consists of a high-power light source directed through a specialized lens which

acts both as a wide-field epi-illuminator and imaging device.

An illumination system useful in the HDFS device is able to deliver excitation light over an area of at least 8.5 by 13 cm at an intensity sufficient to excite measurable fluorescence from that test field (which in most cases will be living cells loaded with fluorescent reporters). The illumination may come from a scanned beam, or be wide-field for simultaneous illumination of the entire area. The imaging system will collect fluorescent light from the entire test area and bring it to focus onto a sensitive imaging photodetector, such as a cooled CCD camera chip.

Screening. The practice of screening large libraries of samples of unknown composition for the few which may contain a compound of specific biological activity is one of the more common methods of new drug discovery. The samples of unknown composition are in most cases biological material, such as plant extracts or microbial fermentation broths. Screening these for biological activity is normally accomplished by performing binding assays or, more recently, functional assays. A binding assay is an attempt to find compounds of interest by identifying those which adhere with some desired affinity to cells or cell products. This can be done using fluorescent, luminescent, or radioactive detection methods. These assays are based not on a biological response, but passive processes of adherence and displacement. They cannot be construed as functional assays or as real-time assays. Another way to determine biological activity is to measure up-regulation or down-regulation of expression of a known gene. This is done by inserting DNA which codes for something which can be readily measured into a cell's genome such that the expression of interest is coupled to expression of the inserted DNA. While this is a true functional assay, it also is not a real time assay. In addition, it is only capable of finding compounds which affect gene expression. In many cases this is not the response of interest.

The CytoSensor described in U.S. Patent No. 4,915,812 and U.S. Patent No. 5,395,503 is a commercial instrument which has been billed as a screening instrument. It is based on the detection of increased cellular proton flux by means of a semiconducting electrode. The instrument is applicable to high through-put screening, but can only detect cellular events that result in changes in extracellular pH. Again, many responses of interest are not associated with changes in extracellular pH.

The growth over the last few decades in the knowledge of cellular signaling has presented extremely rich opportunities for new ways of screening for biologically active

compounds. Armed with knowledge of the biological process which one wants to affect with a new product, it is possible to monitor the actual process as a way of looking for compounds which affect it. The development of fluorescent probe molecules which upon interaction with intracellular signaling molecules (e.g. ions, enzymes, cyclic nucleotides) change their spectral properties has enabled the real-time monitoring of dynamic biological responses within living cells. Most of these probes can be introduced non-invasively into cells and will, depending on the detection system, allow characterization of cellular events in high temporal resolution (microseconds to seconds) and high spatial resolution (nanometers to micrometers). This probe technology, in combination with the technology of cellular imaging which is described below, has had a major impact on cell biology in that it has enabled monitoring of complex, cross-reacting intracellular events that could not be unravelled by conventional invasive biochemical techniques.

Imaging of cellular functions using luminescent probes. Visualization of intracellular function using luminescent (fluorescent or bioluminescent) probes has become one of the mainstay techniques in modern cell biology. Using traditional optical microscopes with quantitative detectors in place of the human eye, both the concentration and distribution in the cell of a variety of intracellular molecules of interest can be measured. While luminescent probes can be measured in large populations of cells using other techniques, imaging is the only way to learn what is going on in single cells or small populations of cells. The imaging capabilities of the HDFS apparatus will be limited to rather low spatial resolution - fluorescent changes will be imaged from the entire field of detector layer up to 8cm by 12.5 cm. When the detector layer comprises living cells, individual cells need not be resolved in the image, only the fluorescent signals from regions in which cells are present.

The imaging times will vary depending on the responses and parameters being monitored. Signaling responses, for instance changes in the level of free calcium in cellular cytoplasm, may first be seen within seconds or minutes following delivery of test compounds to the detector layer. Such changes can be monitored by changes in the fluorescent properties of specific chemical probes, for instance Fluo-3 or Fura 2 may be used to report on cytoplasmic calcium. The way in which these changes develop within cells (time-response profile) is an important diagnostic feature of the signaling processes giving rise to them. Rapid responses are therefore recorded by sequences of images, where the time between images in a sequence is between 0.1 and 30 seconds (depending on the response being

screened for). Transcription mediated events may require minutes to hours to develop. Monitoring may be continuos or intermittent. For slow responses, two images can be sufficient to gauge the level of response, the first taken before application of test compounds, the second after a period during which the response is estimated to have reached its maximum extent.

Controls relevant to the parameters being measured can be incorporated into the test arrays, both as a check for cell responsiveness and as co-ordinate markers within the arrays. The detector layer is continuous and undemarcated, but because of the close apposition of the test array to the detector layer, the center point of a response in the detector layer corresponds to a conjugate coordinate in the test array. It is helpful to have compounds in the test array which will generate known responses at known coordinates in the detector layer. Responses at the conjugate coordinates in the detector layer act as controls for the system's response, against which responses of the detector layer to unknown compounds may be compared; the points of response to control substances also act as reference points in the detector layer from which the coordinates of other responses can be mapped. For example, when bioactivity is determined as the ability to alter the level of free calcium in cellular cytoplasm, common calcium-mobilizing agonists such as carbamylcholine or adenosine trisphosphate are included in the test array at known coordinates.

As another example, when a change in the cellular ratio of inherently fluorescent NAD(P)H/FAD is the biological parameter being assayed, metabolic inhibitors such as KCN or rotenone may be used as a control and marker compounds.

In many instances, diffusion within a thin fluid layer will be involved in many applications of the screening method of the invention, and a concentration gradient will be established from each test point. Those few compounds in a test array which have bioactivity should be detected as spreading rings of response from the focus point of diffusion, within a field of the detector showing no response. The extent of the response areas (measured over time), compared with those from control substances, will provide an indication of potency and solubility of the compound responsible, and also obviate the need to make serial dilutions of test compounds. Toxic or inhibitory substances may also be determined by causing blank sectors in response rings from known agonists. Inhibitory compounds may be determined by their actions on a (pre-)stimulated detector field. Detection of bioactive compounds may incorporate simple image processing to determine the focus, extent and potency/efficacy from

the areas of activity measured in a detector field.

Apparatus

In specific embodiments, the apparatus and method of the invention are as shown in Figs. 1-4. Fig. 1 shows a high energy light source **1**, either a mercury or xenon arc lamp, light from which is collected and collimated by unit **2**, directed through a shutter assembly **3** and passes through a excitation filter-changer **4**. A high-quality light guide **5**, either of fused quartz or a UV-compatible liquid light guide, directs excitation light into the lensing and epi-illumination optics housed in unit 7. Excitation light emerging from **7** evenly illuminates the horizontal detector layer located in the multi-component assembly labeled **10** and **11**.

Further details of this assembly are shown in Figs. 2a-c, 3, and 4. The assembly comprises two solid layers of which **10** is fixed relative to the stage unit **8** which supports it, while layer **11** is moved vertically downward on guide pins (**17** in Figs. 2a,b,c) to bring test compounds into contact with the detector layer. Vertical movement of **11** is controlled by arm **12** driven by unit **13**. Four sprung contacts **14** attached to **12** press upon the frame of layer **11** to drive it downwards as arm **12** descends. A separate drive unit **9** controls position of the stage **8** in the horizontal plane, and also is used to adjust focus by movement along the vertical axis.

Fluorescent light emitted by the detector layer is collected by lensing unit **7**, passes through an emission filter-changer **15** and is brought to focus on the photosensitive surface of an imaging detector housed in unit **16**.

Specified devices (**3, 4, 9, 13, 15, 16**) are controlled by a central processing unit **6** which issues commands to, and collects data and status information from the devices attached to it. Collected data (images) can also be analyzed by unit **6**, or passed to a subsidiary analysis station (not shown). Unit **6** comprises: central processing unit (Intel Pentium chip, or better), RAM, multi-channel serial input/output cards with onboard A/D and D/A converters, one of which cards controls the camera **16** and captures images from it, also a video controller card, VDU, and hard disk memory units.

Figs. 2a,b,c are schematic diagrams of the test stage, which includes a supporting stage **8** with large rectangular central aperture, the shape and size of which is the same as the area labeled **19**. The position of stage **8** is adjusted in the horizontal and vertical axes by the

3-axis positioner **9**. These diagrams are drawn for the specific embodiment in which the detector layer is a layer of living cells growing on the upper surface of the solid transparent component **10**, which also serves to contain the liquid layer **18** which overlays the cells in the detector layer and provides them with necessary nutrients and conditions to keep them alive. The printed array of test compounds **21** is borne on a sheet of track-etched membrane **19** held by a rectangular rigid frame **11**. At the beginning of the screening assay, the array **21** is not in contact with the fluid layer **18**. The array **21** is held away from the liquid layer by pins **17** which pass through holes **24** in the corners of the frame **11** and which, by friction or "click-stops", prevent it from falling (Fig. 2a). At the appropriate moment, arm **12** is moved down by the drive unit **13** and the four sprung contacts it bears **14** exert pressure on the frame **11** moving it down the guide pins **14** and into the liquid **18** below to a position where it is in very close proximity to the underlying layer of detector cells **20** grown on top of the solid substrate **10** (Fig. 2b). Throughout this procedure, the entire area of the detector layer corresponding to the size and shape of area **19** is illuminated and imaged from below by the additional apparatus shown in Fig. 1.

The apparatus can also be used in a second embodiment of the screening method of the invention, where the test array is laid out on the upper surface of component **10**, and components **11** and **19** are a frame and thin transparent track-etched membrane, respectively. In this specific embodiment, the frame **11** is sufficiently deep to contain culture liquid as required to sustain the detector layer of living cells growing on the upper surface of the membrane **19**.

Figs. 3 and 4 are schematics to show the relative positions of the different layers in the test-array/detector layers used in the specific embodiments of the invention. Fig. 3 shows the arrangement in which an array of discrete spots of test compounds **21** on a porous membrane **19** is in contact with a liquid layer **18** overlaying the detector layer **20** which is supported by an optically transparent solid substrate **10**. The compounds fill the parallel capillary spaces **22** in the track-etched membrane **19**. Bioactivity is detected by measuring changes in fluorescence in the detector layer **20** resulting from responses to the diffusion of test compounds through the porous membrane to the detector layer.

Fig. 4 is a schematic drawing of a second embodiment of the screening method in which a detector layer **20** supported on an optically clear porous membrane **19**, and overlayed

by a liquid layer **23**, is placed onto an optically clear solid substrate **10** bearing an array of test compounds **21**. The thin space **18** between components **19** and **10** is filled with solution from **23** which has passed through the porous membrane **19**. Bioactivity is again detected by measuring changes in fluorescence of the detector layer resulting from responses to the diffusion of test compounds through the porous membrane to the detector layer.

Fig. 5 is a schematic illustrating the way in which an array of 1536 compounds can be created on a membrane surface, such as would be useful in the first embodiment described above, by simple transfer printing. Compounds are stored in 16 separate 96-well microtiter plates and defined amounts are transferred simultaneously by a 96-pin printing head to the surface **19**. The contents of each successive 96-well plate are printed at a slightly offset position, generating an array as shown in Fig. 5b after 4 such printing operations, and a full array of 1536 compounds (Fig. 5c) after 16 printing operations. The holes **24** in frame **11** are used to position and guide the completed array on the pins **17** indicated in Figs. 2b and 2c. The process illustrated in Fig. 5 can also be used to transfer an array of test compounds to a solid surface such as would be useful for component **10** in the second embodiment of the method described above.

EXAMPLE

Example 1. Screening of 1536 Test Compounds for Bioactivity.

The following description of the use of one embodiment of the apparatus of the invention in the screening method disclosed. An array of test compounds are supplied in 96-well microtiter plates, as is common practice for compounds produced by methods commonly known as combinatorial chemistry, or for compounds extracted from natural sources. In this example, the compounds are provided in soluble form, and the concentrations and solvents used have previously been tested for compatibility with the apparatus. In this example, 1536 compounds are tested simultaneously against a known cellular target, specifically a G-protein coupled receptor (GPCR) of the Gq type expressed in a transformed cell line. Gq GPCRs give clearly identifiable changes in intracellular calcium when activated.

First, physiologically viable living cells are cultured to a near confluent monolayer in a transparent culture dish (**10**, Fig. 2a-c) in appropriate culture medium and conditions. Immediately prior to being used in the experiment, the cells are loaded with the fluorescent

indicator of free cytoplasmic calcium concentration, Fluo-3 (from Molecular Probes, Oregon). This is accomplished by incubating the cells with a 2 to 5 μM solution of Fluo-3 acetoxymethyl ester (AM) for a period of 10 to 15 minutes, followed by a series of solution exchanges to wash away excess Fluo-3 AM.

The method of transfer of compounds to the track-etched membrane Fig. 2a-c **19** is illustrated in Fig. 5. In this example, 1536 compounds are printed as an array **21** on a single track-etched membrane **19**, from sixteen individual 96-well microtiter plates in the following manner: A 96-pin printing head is used to transfer defined volumes of compounds (in the range 0.05 to 0.5 μl of each compound), one compound per pin, from each 96-well plate in turn (with wash steps between source plates to avoid cross-contamination). Each 96-point print to the membrane occurs in an offset grid, such that 16 print operations are made sequentially on the same membrane and the printed spots of compounds remain discrete and separated from each other (three of these spots are indicated in Fig. 5a, **21**). Fig. 5a shows the result of a single 96-point print operation, Fig. 5b after four such operations, and Fig. 5c the finished array after 16 print operations. In this way, just sixteen print operations (and sixteen intermediate wash steps for a single print head) are sufficient to transfer 1536 compounds to a single test array. The procedure can be readily automated, and multiple copies of each printed sheet made for multiple tests.

Completed arrays are fixed to the pins **17** (Figs. 2b-c) projecting from the culture dish **10** such that they are supported some small distance above the thin fluid layer **18** covering the living cells which form the detector layer. Once the test array is fixed in place over the Fluo-3-loaded cells, the entire assembly is placed onto the test stage as shown in Fig. 2a.

The following events are synchronized by sequential instructions from the computer processing unit **6**. First, the test stage is centered over the lensing unit **7** (Fig. 1) and the detector layer it supports is brought into focus by the motor unit **9**. Fluo-3 is excited by light of 490 nm, and its fluorescent emissions are collected in the range 505-540 nm. The intensity of emission is increased when the dye binds free calcium. Thus the computer brings a 490 nm band-pass excitation filter into line of the light path coming from units **1** and **2** using the filter changer unit **4**. At the same time, a band-pass emission filter for the range 505-540 nm is positioned in the imaging path by unit **15**. The shutter **3** is opened for a pre-determined exposure period (typically 50 to 500 milliseconds), and during this time the whole area of the

detector layer is illuminated with 490 nm light. Fluorescent emission from the Fluo-3 in the cells is collected by the lens **7** and focused into the camera. The camera captures the image and sends it to the processing unit **6** where it is stored and displayed. At regular intervals thereafter, images are captured in sequence by repeatedly opening the shutter **3**. Intervals between successive images are typically in the range 0.5 to 30 seconds, depending on the speed of the response expected. Intervals of 0.5 to 2 seconds are usual and sufficient to sample the dynamics of most changes in cellular calcium. At a predetermined time during this continuing sequence of images, the test array is pushed down the guide pins **17** by the actuating arm **12** and its sprung contacts **14**, driven by unit **13**. In close apposition to the cells in the detector layer, the test array begins to release the compounds it carries. The compounds dissolve into the the liquid layer, and these fall vertically downwards onto the cells below. Because there is only a thin liquid layer between the membrane of the test array and the cells below, there is insignificant intermixing of adjacent test compounds. If a test compound activates cells below it bearing Gq GPCRs, these cells will respond with an immediate increase in free cytoplasmic calcium, and the fluorescence signal from the Fluo-3 dye they contain will increase. The sequence of images collected during the period of the response (which is typically of 1 to 10 minutes duration) will reveal which cells have so responded, and their position in the area of the detector layer will be correlated with the identity of the compound in the array above. An analysis of the entire area of each image in the sequence, performed on-line by the processing unit **6**, yields the following information: the identity of the compound eliciting the response, the profile of the response with time, the intensity of the response, and also the potency of the compound with reference to a chosen standard. The latter information is contained in the radius of the area of cells responding within a particular time, and can be compared directly to a known standard which is included in the array at known points. The use of standard compounds at known points in the array also provides a control for the experiment, and helps to identify coordinates in the detector layer from which other responses can be mapped.

At the end of the screening assay, the sequence of images is stopped, the actuating arm **12** raised, and the test assembly removed. The next assembly is then moved in and the sequence begun afresh. Assembling the test units and exchanging them on the test stage can be automated by appropriate robotic control (not shown in the diagrams).

One of the advantages of the method of the invention is that the method does not require that either the components of the detector layer (e.g. living cells), or the different test compounds, be isolated from one another within discrete chambers or compartments, as is common to all high throughtput screening procedures currently in use or development. The method also removes the need to dispense microvolumes of test compounds during the period of the assay itself. Delivery of test compounds to detector layers is either by direct contact or by simple diffusion across thin liquid films. Delivery and detection becomes a (massively) parallel process.

CLAIMS

What is claimed is:

1. A method for screening test compounds for bioactivity, comprising:

(a) contacting an array of test compounds with a detector layer; and

(b) detecting a detector layer response, wherein a response is indicative of bioactivity.

2. The method of claim 1, wherein the detector layer is comprised of physiologically viable cells.

3. The method of claim 2, wherein the detector layer is supported by an optically clear substrate.

4. The method of claim 3, wherein the reactive sensing surface is held stationary in the field of view of the optical detector and the sample surface is moved into contact with it during the course of the measurement.

4. The method of claim 1, wherein the detection of step (b) is a change in a fluorescence or luminescence property of the cell.

5. The method of claim 4, wherein detection is determined with an illumination system capable of exciting the fluorescence of the reactive surface with any of a number of previously selected wavelengths with defined order and of defined time duration.

6. The method of claim 2, wherein the physiologically viable cells form a monolayer.

7. The method of claim 1, wherein the test compounds are generated on a solid support by combinatorial chemistry.

8. The method of claim 1, wherein the test compound array is generated by one- or two-dimensional gel electrophoresis.

9. A method for high throughput screening of test compounds for bioactivity, comprising:

(a) contacting a solid support comprising an array of multiple test compounds with a cell layer, wherein each test compound comes into contact with a localized liquid which is in contact with a detector layer; and

(b) detecting a response of the detector layer to the test compound, wherein a response is indicative of a bioactive compound.

10. A method for simultaneously exposing an array of test compounds with a reactive sensing surface, comprising the steps of:

(a) contacting an array of test compounds on a solid matrix with a porous membrane which is in contact with a liquid layer overlaying a reactive sensing surface layer; and

(b) allowing the test compounds to diffuse through the porous membrane to the liquid layer overlaying the reactive sensing surface.

11. An apparatus for screening an array of test compounds for bioactivity, comprising:

(a) a solid support comprising an array of test compounds;

(b) a porous membrane; and

(c) a detector layer layer, wherein a liquid layer is between the porous membrane and detector layer layer, and wherein the test compounds contact the detector layer layer by diffusion through the porous membrane.

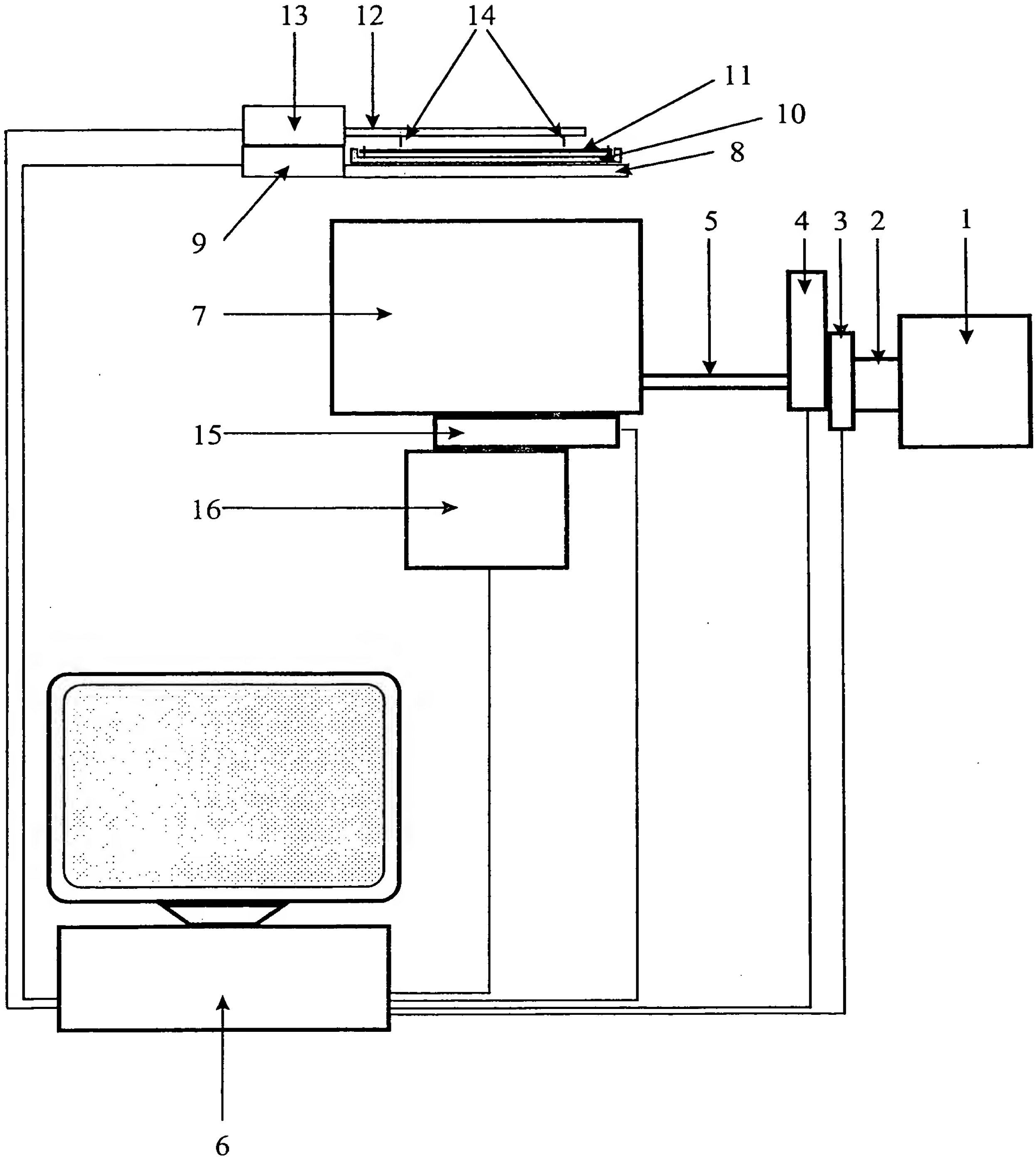
METHOD AND APPARATUS FOR HIGH DENSITY FORMAT SCREENING FOR BIOACTIVE MOLECULES

Abstract

A method and apparatus for screening an array of test compounds for bioactivity by contacting an array of test compounds with a detector layer capable of detecting bioactivity, and detecting a detector layer response. The detector layer is comprised of physiologically viable cells. The method and apparatus allow a large number of test compounds to be simultaneously assayed in parallel.

Fig. 1

Schematic view of equipment; not to scale

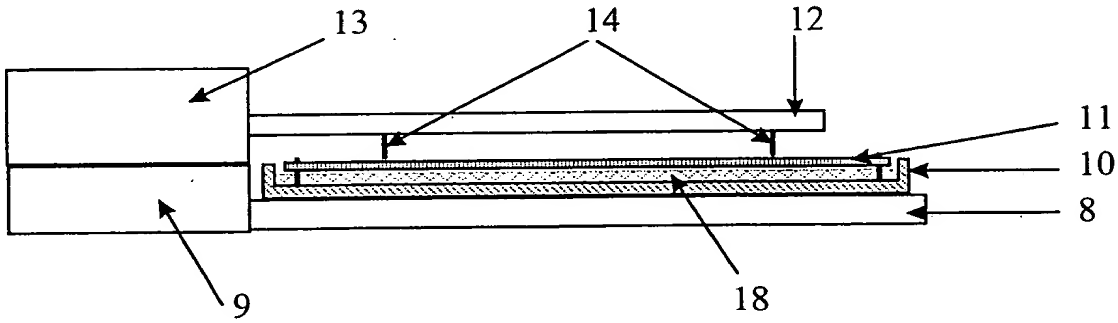


22129DK1 Appendix II

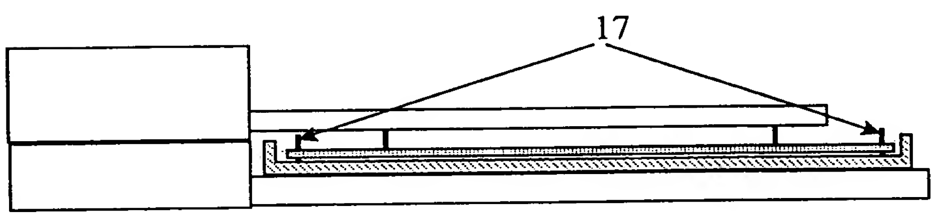
Fig. 2

Side views of test stage; not to scale

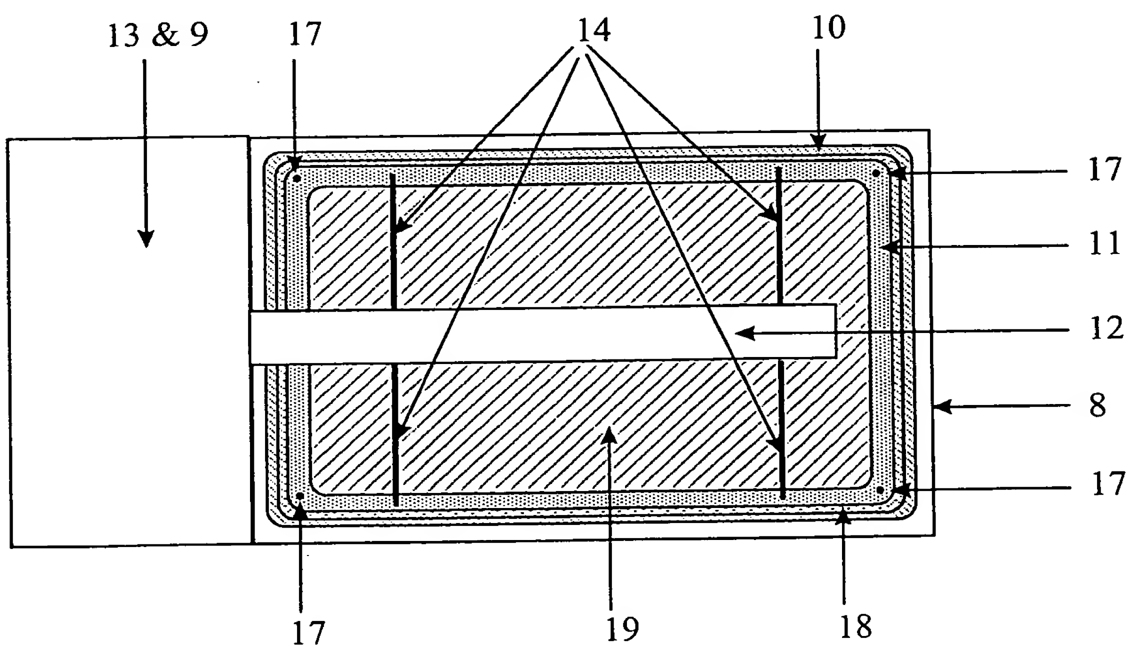
a)



b)



c)



Top view of test stage; not to scale

22129DK1 Appendix II

3-D sectional representations of portions of the test-array/detector layers: not to scale

Fig. 3

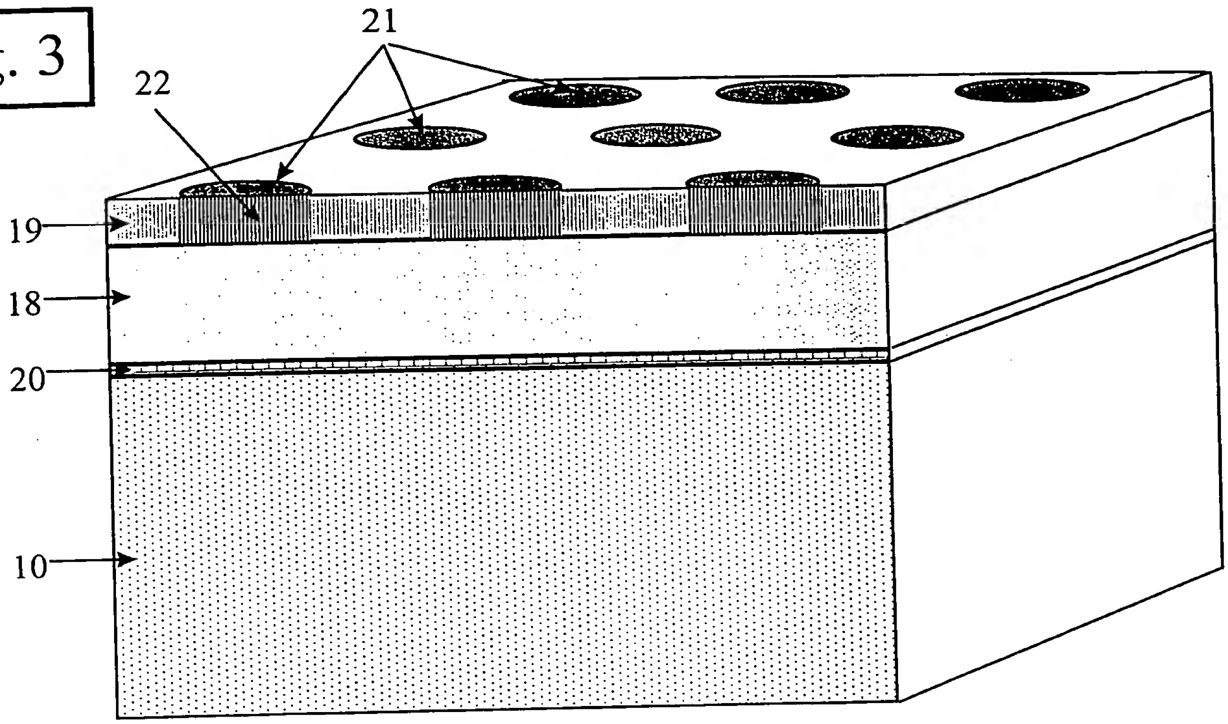


Fig. 4